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CENTER FOR DEVICES AND RADIOLOGIC HEALTH

RADIOLOGICAL DEVICES
PANEL MEETING

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Proceedings By:

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P R O C E E D I N G S

(8:05 a.m.)

Agenda Item: Call to Order and the Chair's
Introduction - Francine Halberg, M.D.

DR. HALBERG: Good morning. My name is Francine Halberg. I have the privilege of being chair. I would like to call this meeting of the Radiological Devices Panel to order.

I would like to remind everyone in attendance if they please sign. The attendance sheets can be found by the door.

I would also like to note for the record that the voting members present constitute a quorum as required by 21CFR part 14.

The panel members will now introduce themselves. We'll all state our specialty, our position and title, institution and whether or not we are a voting member of the panel.

I can start. My name is Francine Halberg. I'm a radiation oncologist with the Marin Cancer Institute, and Associate Professor at the University of California-San Francisco.

Perhaps we'll just go around the table to the right. Dr. Carson.

DR. CARSON: I'm Sandra Carson, a reproductive endocrinologist, Associate Professor of Obstetrics and Gynecology at Baylor College of Medicine, and Chief of Baylor Assisted Reproductive Technology.

DR. HACKNEY: I'm David Hackney. I'm a neuroradiologist, a Professor of Radiology at the University of Pennsylvania. I'm a voting member of the panel.

DR. ALAZRAKI: I'm Naomi Alazraki. I'm nuclear physician, Professor of Radiology at Emory University, and I'm a voting member of the panel.

DR. R. LERNER: I'm Robert Lerner, a radiologist specializing in ultrasound at Rochester General Hospital, and Assistant Professor of Radiology.

DR. YIN: Lillian Yin. I'm the Division Director of Research and Radiological Devices for the Center.

DR. CHOYKE: I'm Pete Choyke. I'm a diagnostic radiologist at NIH. I believe I'm a voting member.

DR. STERNICK: Edward Sternick. I'm a Vice President at Nomas(?) Corporation, and the industry

representative, and a non-voting member of the panel.

DR. GRIEM: I'm Melvin Griem, a radiologist and emeritus professor at the University of Chicago.

DR. SMATHERS: Jim Smathers, medical physicist and Professor of Radiation Oncology at UCLA, and I am a voting member of the panel.

DR. DESTOUET: I'm Judy Destouet. I'm a mammographer in Baltimore, Maryland. I'm not a voting member --

DR. HALBERG: Yes, you are.

DR. DESTOUET: Oh, I am? Thank you.

MR. MONAHAN: My name is Jack Monahan. I'm the Executive Secretary for the panel. I work in the Office of Device Evaluation at the Center.

DR. HALBERG: Jack, do you want to go ahead and read your remarks?

MR. MONAHAN: I note for the record that our consumer representative, Ms. Patricia Whalen, called on Friday to say that she would be unable to attend the meeting due to a death in family. Because of the last minute nature of the emergency, it was impossible to have an alternate

representative appointed to take her place at the meeting today. So unfortunately, we won't have a consumer representative.

I would like read a statement concerning appointments to temporary voting status granted by Dr. Bruce Burlington, Director of the Center for Devices and Radiological Health:

Pursuant to the authority granted under the Medical Device Advisory Committee charter, dated October 27, 1990, and as amended April 20, 1995, Sandra Carson, M.D., Robert Lerner, M.D., and Michael Domanski, M.D. have been appointed as voting members of the Radiological Devices Panel for the February 24, 1997 panel meeting.

For the record, these individuals are special government employees and consultants to this panel under the Medical Device Advisory Committee. They have undergone the customary conflict of interest review. They have reviewed the material to be considered at the meeting.

The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of any

impropriety:

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests; however, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government.

Full waivers have been granted to: Dr. David Hackney and Dr. Robert Lerner for their financial interests in firms at issue that may potentially be affected by the committee's deliberations. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would also like to note for the record that the agency took into consideration matters regarding Dr. Naomi Alazraki and Dr. Hackney. Both Dr. Alazraki and Dr. Hackney reported financial interests in firms at issue, but in

matters not related to topics to be discussed before the panel. The agency has determined, therefore, that Dr. Alazraki and Dr. Hackney may participate fully in today's deliberations.

In the event that the discussions involving any other products or firms not already in the agenda, for which an FDA participant has a financial interest, the participant should exclude themselves from such involve, and their exclusions will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment on.

If anyone has anything to discuss concerning these matters, please advise me now and we can leave the room to discuss them.

I would also like to note that Dr. Peter Choyke from the Diagnostic Radiology Department at NIH, and a member of the CDER advisory committee is joining us today as a consultant to the panel.

FDA also has a conflict of interest policy regarding persons making public statements at advisory panel meetings. Dr. Halberg, our chair, will ask all persons making statements either during the open public meeting, or during open committee discussion portions of the meeting to state their name, professional affiliation, and disclose whether they have any financial interest in any medical device company.

I want to give you the parts of the definition of financial interest in a sponsor company. They include: (1) compensation for time and services of clinical investigators, their assistants and staff in conducting the study and appearing at the panel meeting on behalf of the applicant; (2) a direct stake in the product under review, such as an inventor of the product, a patent holder, or owner of shares of stock; and (3) owner or part owner of the company. No statement, of course, is required from employees of the company.

FDA seeks communication with industry and the clinical community in a number of different ways. First, FDA welcomes and encourages pre-meetings with sponsors prior

to all IDE and PMA submissions. This affords a sponsor the opportunity to discuss issues that would impact the review process.

Second, the FDA communicates through the use of guidance documents. Toward this end, FDA developed two types of guidance documents for manufacturers to follow when submitting a pre-market application. One type of simply a matter of the summary of the information that has historically been requested on devices that are well understood in order to determine substantial equivalents, such as the guidance for the content and review of magnetic resonance diagnostic devices, 510(k) applications.

The second type of guidance document is one that develops as we learn about new technology, such as guidance for the content and review of 510(k) notifications for picture, archiving and communications systems, PACs, and related devices. FDA welcomes and encourages the panel and industry to provide comments concerning our guidance documents.

Finally, I would like to remind you that the tentative dates for the panel meetings scheduled for 1997

are: May 12, August 18, and November 17. I hope you will mark your calendars accordingly.

Dr. Halberg.

DR. HALBERG: Thank you. Before we proceed with the open public portion of this meeting, I believe that Ms. Amanda Norton from the FDA Office of the Ombudsman has a few words to say. Ms. Norton.

MS. NORTON: Thank you, Dr. Halberg.

I asked to speak for a few moments this morning to brief you on some recent filings with the agency that we thought you should be aware of, although they are not going to directly affect today's proceedings.

The agency has received citizens petitions from two companies, Sonus Pharmaceuticals and Bracco Diagnostics, raising numerous issues and requesting that all contrast agencies including Albunex and FS069 be regulated in the Center for Drugs.

In addition, the commissioner of Food and Drug was asked to stay the meeting of this panel. The requested stay of this meeting was denied by the deputy commissioner for operations last week, on the 20th of February, because the

petitions did not support a stay, and because the agency believes it is both valuable and appropriate to continue the ongoing review processes, including this panel meeting, while also considering the important issues raised in the petition.

This panel has been convened to consider scientific issues presented by these pending applications, and to provide expert analyses and opinions for the agency's consideration. As some may recall, this panel in July of 1992, considered a PMA for Albunex, and the product subsequently received marketing approval as a medical device in 1994.

In reviewing the pending applications, the Center for Devices is consulting with the Center for Drugs, as was the case in the initial review of Albunex. This panel's work today, the consideration of the scientific issues raised by these applications, is a vital and integral part of the agency's evaluative process for these products.

Although some speakers in the open public hearing may discuss the issues in the citizen's petition, the issues raised by these petitions are being addressed in other

agency processes. These petitions are public documents, and we hope that all interested persons will file comments to the public docket so that the agency may be as informed as possible.

The agency is carefully examining the wide range of legal, regulatory, administrative and equitable factors raised by these petitions. The agency is also concerned that product applications be processed without undue delay, that the agency's scarce resources be used efficiently, and that fairness and equity obtain to the greatest extent possible.

The agency also appreciates the importance of timely clarification of disputed issues, and plans to deal promptly with the issues raised.

In closing, I would like to say on behalf of FDA how much we value your service on this panel, and the scientific expertise that your deliberations contribute to the work of the agency. I know you have a very full day, and I thank you for this opportunity to speak.

Agenda Item: Open Public Hearing

DR. HALBERG: Thank you, Ms. Norton.

We will now proceed with the open public hearing portion of this meeting. At this time, public attendees are given an opportunity to address the panel, and to present data on views relevant to the panel's activities. We received requests from five individuals who wish to address the panel.

If there is anyone else who wishes to address the panel, would you please raise your hand and identify yourself?

Let me just read some information into the record. I would like to remind public observers that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the chair or the panel.

I would ask at this time that all persons addressing the panel come forward to the microphone and speak clearly as our transcriptionist is dependent on this means of providing an accurate transcription of the proceedings of the meeting.

If you have a hard copy of your slides or your talk available, please provide it to the executive secretary

for use by the transcriptionist to help provide an accurate record of the proceedings.

As the executive secretary explained, we are requesting that all persons making statements either during the open public hearing or the open committee discussion portions of this meeting disclose whether they have financial interests in any medical device company. Before making a presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest in the company, and of course no statement is necessary for employees of the company.

Definition of financial interests in the sponsor company may again include: compensation for time and services of clinical investigators, their assistants and staff in conducting the study and appearing at the panel meeting on behalf of the applicant; direct stake in the product under review, for example, inventor of the product, patent holder, owner of shares, et cetera; or an owner or part owner of the company.

For the record I would note that the FDA received a request on behalf of the first four speakers of this

public portion of the meeting to give their presentation in a specific order. To accommodate the speakers and provide a coherent presentation of the material for the panel and for the audience the FDA has granted this request.

We can now begin the open public portion of the meeting.

Mr. Peter Safir has requested to address the panel. Mr. Safir.

Agenda Item: Peter O. Safir, Kleinfeld, Kaplan, and Becker on Behalf of Bracco Diagnostics, Inc.

MR. SAFIR: I would like to thank the panel for allowing me to speak at this hearing. I am Peter Safir, a partner in the law firm of Kleinfeld, Kaplan, and Becker, and I represent Bracco Diagnostics, Inc., a manufacturer of contrast media for diagnostic imaging.

Bracco is currently investigating an injectable microbubble ultrasound contrast imaging agent which is being regulated by FDA as a drug. The Bracco is substantially similar to Molecular Biosystems FS069, which is before the panel today.

In addition, Sonus Pharmaceuticals and Dupont

Merck manufacture their own injectable microbubble ultrasound contrast imaging agents, which are also being regulated by FDA as drugs.

All of these products share similar indications, modes of action and ingredients, yet FS069 is the only product that has been classified by the agency as a medical device.

Bracco, along with Sonus and Dupont Merck, who will also express their views today, is extremely troubled by the inconsistent treatment of these products by FDA. The regulation of FS069 as a device raises serious issues, both with regard to the legal process by which FDA determines whether a product is a drug or a device, and the scientific standards to which those virtually identical products are held.

With the exception of Albunex and now FS069, both manufactured by Molecular Biosystems, medical imaging contrast agents have always been regulated by FDA as drugs. In fact, on a number of occasions, FDA has specifically determined that ultrasound contrast agents are more appropriately regulated as drugs.

Most recently, on September 18, 1996, FDA accepted for filing an NDA for Ecogen, an injectable microbubble ultrasound contrast agent manufactured by Sonus, which like FS069 contained perfluoro(?) chemical gas within the microbubbles. Nevertheless, FS069 continues to be regulated as a device.

As will be explained in greater detail by the representative of Sonus, new drug applications for microbubble ultrasound imaging agents may require the sponsor to collect and submit significantly more scientific data in support of the application than do pre-market applications for similar medical devices.

The Center for Drug Evaluation and Research in general requires that a sponsor conduct additional studies to demonstrate the safety and effectiveness of new drugs that are not generally mandated by the Center for Devices and Radiological Health. While this is appropriate with regard to many devices, it is clearly not appropriate when the products regulated by each center are essentially interchangeable.

Accordingly, while we understand that the panel

has no role in the jurisdictional issue before FDA, it is essential that when voting on the Molecular Biosystems application today the panel recognize that it is setting the standard for the safety and efficacy of this class of product, however it is to be regulated by FDA.

If the committee determines the data supporting the FS069 PMA are sufficient to address FDA's concerns regarding safety and efficacy, the panel will be announcing to the scientific community that any additional information required by the Center for Drugs for approval of other injectable microbubble ultrasound imaging agents is not necessary, and that the data contained in the FS069 PMA would be sufficient for all of these products.

The inconsistent position taken by FDA with regard to the regulation of ultrasound contrast media has also led to uncertainty among manufacturers as to the proper route to approval of such products. Each day that FDA fails to clarify the correct categorization of these products, manufacturers of ultrasound contrast agents are placed in increasingly disadvantaged positions as they have no way of knowing what the agency will ultimately decide with regard

to any given product, and what studies will ultimately be necessary for approval.

The delay in approval imposed on those sponsors who fail to file with the correct center, or who postpone filing their application until the agency's position is determined will make it much more difficult, if not impossible for those companies to bring their products to market in a timely manner.

For all of these reasons, we believe it is essential for FDA to clarify the proper regulatory route for approval of ultrasound contrast agents prior to acting on any current pending applications, including that of FS069. Bracco and Sonus have already filed citizen's petitions with agency raising this issue.

Moreover, we request the panel consider that when voting on the FS069 application before you today, whether any additional data that may be requested by FDA's Center for Drugs is necessary to establishing the safety and efficacy of these products.

Thank you for the opportunity to speak to this panel. Bracco looks forward to participating in any future

dialogue concerning the proper classification of these products.

DR. HALBERG: Thank you, Mr. Safir.

The next speaker is Dr. Steven Quay.

Agenda Item: Steven Quay, M.D., Ph.D., President
Sonus Pharmaceuticals

DR. QUAY: Good morning panel members, members of FDA, ladies and gentlemen.

I am Dr. Steven Quay. I am President and CEO of Sonus Pharmaceuticals. My background that is relevant is included on this slide. I have an M.D. and a Ph.D. from the University of Michigan. I was on the faculty at Stanford for six years, during which time I was the founder of Salutar(?), a company developing MRI contrast agents. In 1991, I became the founder of Sonus, and until last month was a non-voting member of this panel. I was the industrial representative.

I have over 30 patents in contrast agents, and invented and developed 2 FDA approved MRI contrast agents. Disclosure -- I invented and developed Ecogen, and ultrasound contrast agent, under review by CDER. We have

filed a citizen's petition to request that FDA regulate all ultrasound contrast agents as drugs, requiring approval by CDER before marketing in the United States.

Basically, I would reiterate a key point that was made in the last speech. This slide contains six products that are under development as ultrasound contrast agents. The left-hand column contains the sponsor, the product name, the indication of all six's echocardiography. The fluorocarbon or sulfur hexafluoride fluorinated chemical entity is shown the third column. You will notice three of these products have identical C3F8 active ingredients including FS069.

All of these are administered as IV-aqueous(?) fluids. They are all manufactured under largely the same conditions. Five of the six are being regulated as regulated as drug; one as a device.

In 1992, CDER filed a petition requesting a jurisdiction be set for our product, the fluorocarbon ultrasound contrast agent, Ecogen. After a two month review, CDER and CDRH determined that Ecogen should be treated as a drug. I believe this was a precedent setting

event, and should have set the stage for FS069 to also be treated as a drug.

I would like this panel to consider the question, shouldn't products with the same indication, the same active ingredient and administered in the same fashion be developed to and approved by the same standards?

I would like to offer some points to consider in the review of ultrasound contrast agents that have come up in the development of Ecogen and the other contrast agents I have been involved with:

(1) one point is the complete non-clinical study package. I will indicate what I mean by that in a moment;

(2) trials to support product indications should document reproducibility;

(3) the initial product labeling should be broad enough to reduce off label use;

(4) the patient database should be large enough to identify rare adverse events; and

(5) adverse event reporting should be standardized and centralized at the FDA.

These are some -- these are not all of the studies

-- but these are some of the important studies that I believe should be included in a non-clinical package: single and multiple dose toxicity studies in rodents and non-rodents, cardiovascular toxicity studies.

Especially with fluorocarbon containing products, a special toxicity study, a special pulmonary toxicity study that the industry name of hyper-inflated, non-collapsible lung syndrome study. Fertility and reproduction studies are typically required for these class of agents.

Mutagenicity studies including: Ames, mouse lymphoma studies, chromosomal aberration and micronucleus assays. Finally, pharmacokinetics in ADNEY(?) studies.

For those who may not be familiar with the hyper-inflated non-collapsible lung syndrome system, I would like offer you some information here. The problem here is quoted by Dr. Leland Clark, who was the inventor of the use of fluorocarbons as blood substitutes, and continues to work actively in this field.

The hyper-inflationary non-collapsible response of the rabbit lung to intravascular fluorocarbon emulsion is a reproducible physiologic phenomena and can be used as a

criterion of safety. If practical methods cannot be found to prevent or counteract HNCL, then only fluorocarbons boiling above 150 degrees centigrade can be considered safe.

FS069 contains profluoropropane with a boiling point of -39 degrees. It is a fluorocarbon emulsion, much like these emulsions.

The questions for this panel:

(1) Could HNCL have caused the rabbit deaths that were recently reported by Yale University radiologists studying FS069?

(2) Shouldn't FS069 be studied for HNCL in a GLP rabbit study before recommending approval?

(3) Finally, shouldn't this panel require human pulmonary safety studies, including pneumotachometry, spirometry and other pulmonary function tests as required by CDER?

Trial to support product indications should be replicated with at least two adequate and well controlled trials. The problem, historical industry precedents, FDA regulations and GCP guidelines support the requirement to demonstrate reproducibility of clinical data by performing

at least two adequate and well controlled trials for each approved indication.

The question for the panel, shouldn't the sponsor be required to demonstrate reproducibility of safety and efficacy in echocardiography with FS069 before the panel recommends approval by requiring the performance of at least two adequate and well controlled trials as are required for all contrast agents reviewed by CDER.

Next point, initial clinical studies and product labeling should be broad enough to reduce off label use, that is both echocardiography and radiology studies should be included in the database.

The problem, ultrasound contrast agents can be used not only in the 14 million echo studies each year, but up 18 million radiology studies. FS069 has been studies in radiology, and the sponsors indicate an intent to file these studies at a later date.

Current drug standards, drug policy required that Ecogen be studied in both echo and radiology before our NDA was filed to prevent potential uncontrolled off label use in radiology.

Question, do the animal deaths previously noted in radiology liver tumor model studies suggest that this patient population could have a different safety profile compared to cardiac patients? Shouldn't this panel require the sponsors to complete studies supporting the use of FS069 in radiology before approval to avoid off label use in an indication where there has never been an FDA approved ultrasound contrast agent?

The patient database should include at least 400 patients to support safety labeling concerning adverse event frequency. One purpose of phase 3 trials is to provide label guidance to physicians concerning rare adverse events, sometimes defined as events occurring at the 1 percent incidence level.

Biostatistics and historical precedence in contrast agent development supported a development model that a minimum of 400 patients are needed in phase 3 to provide adequate labeling. Isoview(?), omniscan and cardiolite are just a few of the contrast agents, and representative of x-ray, MRI and nuclear medicine products that were each studied in more than 400 patients in phase 3.

The reasoning is if an adverse event exists in a patient population at a 1 percent incidence level, a clinical trial of 400 patients will identify such an event with a very high power, 0.98. A trial of 203 patients can detect only those adverse events with an incidence of greater than 2 percent. Thus, a 203 patient study could miss adverse events below the 2 percent level. I'll remind you that an adverse event with an incidence of 2 percent would involve a 20,000 patients per million studied.

The question for this panel, is a single 203 patient study with FS069 sufficient for approval when the industry standard for contrast agents and CDER policy is at least 400 patients?

This slide is included in the package for the panel. It is a summary of the device versus the drug adverse event reporting standards. In devices, deaths and serious injuries are reported within the statutory time limits as set forth in this table. In the area of drug adverse events, the important distinction I wish to make for this committee is that non-serious adverse events also require reporting to the FDA, unlike with devices.

Adverse event reporting should be centralized at FDA with other contrast agents in CDER so that non-serious adverse events can be reported.

Question for this committee, do practicing physicians have a right to know about safety matters other death or serious injury when they give a diagnostic contrast agent, which by definition must have a low cost/benefit ratio?

Should CDER be given the responsibility for FS069 to assure complete post-marketing safety monitoring along with other fluorocarbon agents?

Remember, an approval of FS069 as a medical device will mean that the FDA and practicing physicians will never learn about non-serious adverse events with this contrast agent.

Mr. Davis is now going to go through four pages of Orange Book filings. These are products which are classified as drugs in the diagnostic business. You will notice that a large number of them, 11 of 43 in fact are manufactured by Mallinckrodt, the potential marketing company for FS069. So clearly when Mallinckrodt develops

agents for themselves, they develop them as drugs. We're including all of these in case you want to have a record of them.

This list contains 43 x-ray, MRI and nuclear medicine contrast agents from 11 companies which were developed to the drug standards which I just reviewed for you. There are 5 fluorocarbon ultrasound contrast agents under development as drugs.

No foreign governmental agency has ever regulated any contrast agent as a medical device. We believe FS069 will have to be regulated in Europe for example, as a drug and not a device.

I have illustrated some of the possible deficiencies in the FS069 development program when it is compared to CDER drug standards. My question for the panel, shouldn't FS069 be developed to, and approved by the same standards as other products with the same indication, and the same active ingredients.

The FDA acknowledges that the device versus drug classification of FS069 is still under internal review. Ms. Amanda Norton just made that point. Shouldn't this

committee postpone voting on approval until the committee is given the appropriate criteria to use to judge safety and efficacy, since clearly CDER and CDRH have different criteria for safety and efficacy?

Other options would include the recommendation by the committee to transfer to CDRH this product. This would insure both pre-market development standards and post-market safety surveillance. An alternative would be for the committee to ask CDER to give the official FDA criteria -- don't take my word for it, get the official FDA criteria -- for contrast agent development, and apply them to the review of FS069.

The committee might then consider tabling the question of voting on approval today, and to await if there are any official deficiencies. Another meeting could then be rapidly scheduled in which approval could be considered. This would not, however, solve the post-market safety surveillance problem.

Thank you very much.

DR. HALBERG: Thank you, Dr. Quay.

The next speaker is Mr. Alan Carpenter.

Agenda Item: Alan Carpenter, Vice President of
Clinical Research, Regulatory Affairs, and Discovery
Research, Dupont Merck

MR. CARPENTER: Thank you, Dr. Halberg, members of
the panel. My name is Alan Carpenter. I'm a Vice President
of R and D at the Dupont Merck pharmaceutical company.
Dupont Merck, in collaboration with its partner the MRX
Pharmaceutical Company, is involved in the development of an
ultrasound contrast agent referred to as DMP115 or
Aerosomes(?), which is being regulated under the Center for
Drugs.

Thank you very much for giving me the opportunity
for Dupont Merck to present its views on some of the issues
that are important for FDA consideration with respect to all
contrast media. Our company believes the standards for
evaluating safety and efficacy of this class of drugs are
inconsistent within FDA as a result of the current split in
jurisdictional review between the Center for Devices and the
Center for Drugs.

Dupont Merck, in collaboration with MRX
Pharmaceuticals, as well as several other companies in the

industry have ultrasound contrast agents which are being developed and regulated under the Center for Drugs, however, FDA has accepted for review and approval the ultrasound contrast agent under consideration today, FS069, as a device.

Despite the controversy regarding the proper classification of these materials, as Ms. Amanda Norton alluded to earlier, it is probably not appropriate for this panel to be considering the policy issues at this particular time, however, I would like to speak with some attention to the issues around what is relevant around the scientific data supporting the approvability of what we believe should be done for ultrasound contrast media.

It is the belief of Dupont Merck that the FDA should decide on common standards for proofs of safety and efficacy for this class of materials and how they are reviewed and approved. In the classification of contrast media under consideration today as a device has led to this panel's review of this particular agent, however, at the same time as mentioned by the previous speaker, there are several which are being developed as drugs with somewhat

different criteria being established for safety and efficacy.

Dupont Merck, together with MRX, has carried out extensive pre-clinical safety evaluations of DMP115, as requested by the FDA, which are typically required of repeat administration drugs. This includes a full battery of in vitro and in vivo genotoxicity studies and teratogenicity studies.

Furthermore, in its phase 3 studies, Dupont Merck, at the request of the FDA, has agreed to undertake three days of safety follow-up in a large fraction of its enrolled patient population. It is interesting to note that the active drug substance of FS069 is perfluoropropane, a heretofore unapproved material for intravenous administration.

This is the same active drug substance which is in DMP115, which is being developed by Dupont Merck. It is the expectation of industry and the public as well that similar safety assessments should be uniformly applied across both CDRH and CDER reviews of ultrasound contrast agents, particularly for the same mechanism of action and the same

active drug substance, in this case perfluoropropane.

Regarding efficacy standards for ultrasound contrast agents being regulated as drugs versus devices, different standards also appear to exist. Dupont Merck and other companies developing ultrasound contrast agents have been directed to conduct phase 3 efficacy studies in both echocardiographics, structural image enhancement, as well as cardiac functional measurements.

Indeed, Dupont Merck was advised by CDER during its pre-phase 3 meeting that a structural enhancement trial versus Albunex was not acceptable standing alone as a proof of clinical utility, and that cardiac functional measurements with contrast enhanced echocardiography versus an acceptable standard of truth should be applied in order to show clinical effectiveness.

As a result, the Dupont Merck trials in phase 3 involve four separate independent and well controlled trials, two for demonstrating structural enhancement utility, as well as two trials for demonstrating improved echocardiography functional measurements, that is, left ventricular injection fracture measurements.

According to the FDC pink sheet reports, July 2, 1996, a single phase 3 trial has been included in the PMA currently under review for the ultrasound contrast stage in FS069. The standard expectation within FDA, except for situations such as AIDS or cancer or other life threatening diseases is that two adequate and well controlled trials are required to support a claim for efficacy.

Our concern is that the requirements for the proof of efficacy for this class of materials should be uniformly developed and applied, particularly for the same mechanism of action and the same active drug substance. The concerns of Dupont Merck are not new on this issue. We have expressed these concerns and pointed out these differences previously to FDA, dating back before the filing of this PMA for FS069.

We have been advised that the agency will apply common criteria for the establishment of safety and efficacy of these materials. Our position is simple. We request the commissioner's office to establish, with CDRH and CDER, agreement on applying uniform standards, both clinically and pre-clinically for establishing safety and efficacy of all

the materials within this class.

This action is needed to assure furtherance of the basic FDA mandate which is protecting the safety and welfare of the public by uniformly regulating new drug substances such as ultrasound contrast agents whether they are reviewed by CDER or CDRH. We believe this agreement on safety and efficacy standards for review of all ultrasound contrast agents must be established prior to approval of any new contrast agents.

Thank you very much for your time and attention.

DR. HALBERG: Thank you, Mr. Carpenter.

The next speaker is Dr. Scott Gazelle. Dr.
Gazelle.

Agenda Item: G. Scott Gazelle, M.D., M.P.H.,
Brigham and Womens and Massachusetts General Hospitals

DR. GAZELLE: Good morning, members of the committee, ladies and gentlemen. Thank you for giving me the opportunity to speak today.

My name is Scott Gazelle. I'm a radiologist at the Massachusetts General Hospital. I'm also Associate Director of the MGH Center for Imaging and Pharmaceutical

Research, and I serve as co-Director for the Joint Brigham and Womens Hospital-Massachusetts General Hospital Center for Clinical Trials. This center was established primarily to perform industry-sponsored clinical trials of new drugs and devices, to help in the approval process.

By way of disclosure for potential conflicts of interest, I can say that in the last year I have served as a principal investigator for industry-sponsored trials sponsored by Bracco, Nicomed(?), Mallinckrodt Pharmaceutical, and that my research has been sponsored by another company called Acuser(?) Incorporated, and previously by Nicomed and Sterling. So I have worked with most of these companies.

I am here today, however, to express my own opinions. I think that if anyone, I speak for fellow radiologists and the medical community.

My purpose and the intent of my comments is to suggest that the approval process for contrast agents, be they devices or drugs, should be a uniform one, and specifically to argue that it is very difficult reading the specific criteria for drugs and devices to know whether any

of the agents under approval or under consideration for approval or previously approved are strictly speaking drugs or devices.

I do feel that the fact of the matter is all of the agents, with one exception, have been approved as drugs. I think it is therefore, important that all further agents continue to be approved as drugs. I think that there are a number of reasons for this.

As I have said, I have a difficult time knowing whether any of the agents currently under approval are strictly speaking, drugs or devices, and I think arguments - - very coherent and cogent arguments -- could be made in either direction.

I don't think the majority of radiologists out there know the difference. That is, I don't think the majority of us using these agents -- and I perform ultrasound on a daily -- know whether one contrast agent was previously approved as a drug or a device, or whether currently investigated agents are being considered as drugs or devices.

What we know and what we expect is that they are

being considered by the government, by the FDA for approval for use as a contrast agent, and we expect that that process be consistent.

I think that this is true of the public. The public has the right to expect that contrast agents which are approved, which are stamped as being okay for public use, are approved in a consistent manner, and that when one agent is approved next to another agent which is approved, they have withstood the same rigorous criteria for approval.

I think that it is misleading to the public to see two agents that are for the same use, and to their knowledge the same sort of indications, and basically the same type of an agent approved, and not know that one is approved under different standards and criteria.

I do not know the evidence which either Sonus, Bracco or MBI and Mallinckrodt have submitted for approval, because to the best of my knowledge, this was not public record. I do know or feel certain in arguing that it is different. I think that even within say the drug pathway, the data that is required from one agent to the next is different, and is tailored to the specifics of the agent,

and concerns that there might or might not exist regarding the safety of that agent.

I do feel that by centralizing the authority for requiring data within one committee, the public, the medical profession, and frankly the pharmaceutical industry is best served. I think even the pharmaceutical industry has the right to expect going into the process that the demands placed on them will be similar, and that starting with the development of an agent, they should know what lies ahead.

It's not my intent here to specifically argue for or against any one particular agent, because frankly I think FS069 is a pretty good drug, or a pretty good contrast agent. To the extent that I know about the other agents under approval right now, I think that they are all pretty good, and I don't think any of them are going to be the final answer in ultrasound contrast agents, but all of them offer us as radiologists, something that is not available on the market today, and something which I believe would help our patients were we to have them available.

I'll summarize by saying that I feel that all of us, meaning physicians, the public and even the

pharmaceutical industry for whom I do not directly speak, have the right to expect consistency. Given the inconsistency in the approval processes, I would urge the committee to seriously consider whether or not it is appropriate to approve FS069 today as a device, or whether or not it would be more appropriate to defer, and rechannel that agent through the drug pathway.

Thank you very much.

DR. HALBERG: Dr. Gazelle, could you state for the public record who is reimbursing your travel expenses?

DR. GAZELLE: Yes, Bracco Diagnostics has paid for my travel down to Washington. I am not being paid in excess of my travel to speak here today. Frankly, as much as Washington is a nice town, I would rather be home.

DR. HALBERG: Thank you, Dr. Gazelle.

The next speaker is Dr. Kenneth Widder. Dr. Widder.

Agenda Item: Kenneth Widder, M.D., CEO and Chairman of the Board, Molecular Biosystems, Inc.

DR. WIDDER: Good morning. I'm Dr. Kenneth Widder. I'm Chairman and Chief Executive Office of

Molecular Biosystems.

My comments are intended for the panel members in particular, but of course for all attendees additionally.

A lot has been said this morning about the status of MBI's ultrasound imaging agents Albunex and FS069, the latter being our second generation device imaging agent. Importantly, the comments made are wholly irrelevant to the panel's deliberations.

MBI's microspheres differ from other companies' microbubbles not only in composition, but also the fact that FS069 is not an emulsion. What is important today is the quality of MBI science, and the results of complete and well done clinical studies. These considerations should be the focus of the panel's attention, and not the unfortunate arguments intended to sidetrack an orderly panel and PMA review process.

What the panel may not be aware of is that MBI worked closely with the FDA to design and execute its studies. MBI's clinical development plan resulted from detailed discussions with the agency's scientific reviewers. Lead review was placed in the Center for Devices and

Radiological Health in March of 1996, by FDA's product jurisdiction officer.

It was clear that consistent with the Safe Medical Devices Act of 1990, every center of FDA with something to contribute to the evaluation of FS069 would have the opportunity to be involved in the design of studies, and ultimately their review. In other words, consistent with the law, the collective expertise of the FDA could contribute to MBI's or for that matter, any other company's pre-market approval submission.

As a result of its intensive interaction with the FDA, MBI is confident that its studies for FS069 are comprehensive and of the highest quality, and trust the panel and FDA will agree. We look forward to today's presentation to the panel, and the panel's deliberations.

MBI is committed to being responsive to questions and suggestions from the panel and FDA. Science, and not politics should define today's activities, and we heartily endorse the panel's mission of scientifically and medically evaluating the PMAs on your agenda.

I appreciate the opportunity to address you, and

thank you for your attentiveness.

DR. HALBERG: Thank you, Dr. Widder.

Before we begin the panel discussion, I believe Dr. Kimber Rickter, Deputy Director of the Office of Device Evaluation, would like to say a few words. Dr. Rickter.

DR. RICKTER: I'm Kimber Rickter, and I am Deputy Director in the Office of Device Evaluation in CDRH at FDA.

I would just like to comment that this morning we heard from both the agency on the public, comments about FDA's regulation of contrast media agents. At this time, I would like to stress that this advisory panel has been convened to discuss the scientific merits of the data that is contained in a PMA supplement, this morning's session, and a PMA for the afternoon session.

We ask that the panel focus its attention on the scientific data presented in these two marketing applications, and make recommendations on the safety and effectiveness of these products.

Thank you, Dr. Halberg.

DR. HALBERG: That concludes the open public portion of the meeting. We will now proceed with the main

task of the morning. The panel is considering a new indication for Albunex.

Let me now introduce Dr. Jennifer Kettner, who will begin the company's presentation of the information contained in the PMA supplement that we are considering today.

Agenda Item: Mallinckrodt Presentation for P900059/S04, Introduction/Agenda - Jennifer Kettner, R.Ph.

DR. KETTNER: Good morning, ladies and gentlemen. My name is Jennifer Kettner, Senior Regulatory Affairs Associate for Mallinckrodt.

We want to thank the FDA Center for Devices and Radiological Health and members of the panel for inviting us here today to present a summary and supporting information for the use of Albunex in assessing fallopian tube patencies.

At this time, I would like to have some hard copies of our presentation and this afternoon's presentation passed out to the members of the panel and the FDA for their convenience.

Today's presenters include Dr. James Wible,

Research Associate, Mallinckrodt, and Dr. Anna Parsons, Associate Professor, Department of OB/GYN, University of South Florida.

Also in the audience are other representatives from Mallinckrodt: Dr. Oye Olukotun, Vice President, Medical and Regulatory Affairs; James Keller, Director, Regulatory Affairs; Dr. Raymond Schmelter, Director, Medical and Regulatory Operations; Dr. Gary Stevens, Director, Biostatistics; Dr. Gary Brandenburger, R&D Ultrasound Contrast Media; and Dr. Linda Fletcher, Associate Director, Imaging.

In addition, we have two consultant physicians in the audience who can answer questions from the commission's viewpoint, Dr. Jodi Lerner, a gynecologist from Columbia Presbyterian Medical Center and Dr. Jeanne Cullinan, a gynecologist and radiologist from Vanderbilt University Hospital.

Following my introduction, Dr. Wible will summarize our pre-clinical data, and Dr. Parsons will explain the sono-HSG procedure, and summarize our clinical data demonstrating safety and efficacy.

Mallinckrodt and Molecular Biosystems of San Diego, California are involved in a partnership where MBI develops and manufactures ultrasound contrast media, and Mallinckrodt markets and distributes these products, and developed this indication.

Albunex is a sterile suspension of air-filled albumin microspheres that is echogenic immediately following manufacture.

Marketing authorization was first obtained in the United States in August 1994. Other countries that have approved this product for marketing: U.K, Sweden, Finland, Japan, Mexico and Canada for the first indication, cardiac imaging agent.

To this date, there are approximately 27,000 units that have been distributed in the United States, and this equates to approximately 17,000 patient administrations.

The indication we are seeking today is Albunex is indicated for use with transvaginal ultrasound to assess fallopian tube patency.

Due to our limitation on time, we would ask that you please hold your questions until the end of our

presentation.

At this time, I would like to introduce Dr. James Wible, who will continue with the preclinical safety studies.

Agenda Item: Preclinical Toxicology - James Wible, Ph.D.

DR. WIBLE: Good morning.

During the original submission of the PMA package for Albunex, a complete package of preclinical studies was included. These studies demonstrated that under acute and repeated administration of Albunex, no adverse effects were seen.

In teratology studies in both rabbits and rats, no teratogenic effects were observed.

In vitro studies demonstrated that Albunex has complete compatibility in human blood.

Injected intravenously or intramuscularly, Albunex did not show any inflammatory responses.

In guinea pigs and non-human primates, Albunex was demonstrated not to be a sensitizer; however, as one would expect, Albunex being composed of a human protein and

foreign to these species, it is antigenic.

In an Ames test, Albunex was demonstrated to be non-mutagenic.

For this specific indication of fallopian tube patency, we have two different studies that assessed the potential irritative effects of Albunex. One was completed in rabbits, where Albunex was instilled into the fallopian tube and uterus. In addition, two controls were also used. These were instilled unilaterally into the fallopian tube in uterine horn.

The animals were assessed at two different time points, and the results demonstrated that there were no gross nor histological changes produced by Albunex; however, in the Albunex group there was one focal area of inflammation in skeletal muscle tissue. This was consistent with needle trauma that was produced by supplemental administration of anesthesia.

Data from this study indicates that Albunex caused no inflammatory response in or around the reproductive tract.

In rats we also assessed the potential irritative

effects of Albunex when instilled into the peritoneal cavity. Again, Albunex and two controls were used in this study. Material was injected intraperitoneally and assessed at three different time points.

Again, data showed that there were no gross changes nor histological changes produced by Albunex. Again, we conclude that Albunex caused no inflammation in the peritoneal cavity or abdominal organs.

We feel that the data that we have presented is compelling and demonstrates that Albunex is non-toxic, non-teratogenic, non-genotoxic and non-irritating. When instilled into the reproductive tract of female rabbits, there were no adverse effects; no indication of inflammation. Following intraperitoneal injection into female rats, again, there was no indication of inflammation or infection.

What I would like to do now is turn the rest of the presentation over to Dr. Anna Parsons, for the clinical data.

Agenda Item: Clinical Studies - Anna Parsons,
M.D.

DR. PARSONS: Thank you.

My name is Anna Parsons. I'm an Associate Professor in the Division of Reproductive Endocrinology in the Department of Obstetrics and Gynecology at the University of South Florida. Mallinckrodt has paid for me to come here today, and paid for me as a consultant to assist them in this presentation. I was investigator in the phase 2 and 3 trials of Albunex for this indication.

I am very grateful to the panel for their consideration of this new application of Albunex, since it is the only available ultrasound contrast agent to clinicians in the country today.

About one-third of women who seek treatment for infertility have damaged tubes. The current method of screening for damaged tubes involves the use of ionizing radiation, and only shows us the lumens of the uterus and the tubes, not the pelvic organs themselves. So therefore, we are irradiating gonads in women who seek to use their ovaries for reproduction.

This is the hysterosalpingogram or the HSG. It's a procedure we have been doing 50 years. It is a fairly

good screening test. It requires experience and attention on the part of the interpreter. It's utility has a wide range of efficacy because of this.

I'm going to describe the technique, which has been developed involving the placement of a cervical balloon catheter in cervix of the uterus. We use transvaginal ultrasound to do what we call the sono-HSG, or hysterosalpingogram.

The first step after putting a small balloon catheter in, a very similar catheter to that -- the same catheter in fact used for the standard HSG. After that, saline is instilled to outline the uterine cavity, because saline, a negative contrast agent with ultrasound, is useful for delineating soft tissue details, whereas with the small lumens of the tubes, a positive contrast agent is required.

Our criteria for tubal patency involves scanning of the proximal tube as the agent leaves the uterus. If we see forward flow in tube for more than 10 seconds, without the formation of a hydrosalpinx, we assume tubal patency.

The second criterion is observation of spill of the agent into the ambient peritoneal fluid or saline around

the ovary in order to confirm contiguity between the tube and the ovary, something that is not possible using either the hysterosalpingography or even laparoscopy, which has been considered the gold standard of tubal patency.

The reason is that laparoscopy, women are on their head and turned in the downward position, and the uterus is being manipulated. Only with ultrasound in real time can we observe this relationship in vivo and in situ.

Now I'm going to show you a videotape that demonstrates how we use this.

You can see this is a uterus that contains a polyp. This polyp is in a position where we expect a pregnancy to implant, and it is beautifully outlined with saline infusion. Every millimeter of the surface can be seen using this technique with practice.

This is not the contrast agent. This is just cervical mucus with a little air. You see the utility of using bubbles as a contrast agent for ultrasound; they are very bright.

Now when we infuse the Albunex, it fills the cavity, and therefore this is not particularly useful for

looking at the details of the uterine cavity, because it simply blocks out the surface details. What it is great for is showing the fine lumina of the tube. In the flow you can see coming down the proximal tube, and then later observation shows spill into the small pocket of fluid around the ovary.

It is unambiguous and extremely quick to obtain in most patients. This is more reliable for the presence of patent tubes. You can see here is the uterus, and here is the contrast agent spilling around the uterus as it flows out the tube. If we focused on the proximal to here, you would see constant flow in this area.

In the case of bilateral proximal obstruction you see here first the saline is used again to carefully delineate the cavity, because we want to achieve at least as much information as we do from the standard HSG. You can see that the saline vaguely outlines the proximal tube. Here you see the Albunex shows absolutely no flow through the intrastial part of the tube, and there is no flow around the uterus or the ovary.

Here is the case of a unilateral proximal

obstruction. There is contrast in the cavity of the uterus here. Here is proximal flow out the right. It's very easy to see. You can watch carefully, there is ambiguity if there is no saline around the pelvic organs with the appearance of bowel sometimes. That's why we prefer to have contrast.

Here you can see on other tube, there is a collection of the Alburnex here that does go anywhere. It does not move. It is simply sitting there shimmering, trapped in the tube. One of the wonderful features of this is that is an evidenscent(?) effect, and it clarifies and allows outlining of the tube with the saline it becomes.

Now here is an abnormal right tube, and you can see proximal flow here. You can also confirm proximal flow by a non-pulsatile post-doppler signal, but that is not really necessary in my opinion.

There is no spill out of this tube around the ovary, and the reason is the contrast agent effect has been diminished by the fact that there is a stricture in this particular tube, and it fails to maintain its appearance as it passes through this stricture, although it is technically

patent.

Now you can see bilateral spill. This is the opposite tube that happens to be coming across. This is only method, as I said, in which we can see spill in the woman as she lies on the table in a normal position and awake.

There have 3 phase 2 trials performed on this agent; a total of 21 patients, some in the United States and 7 in Europe. These patients were unblinded comparisons between undergoing HSG for infertility evaluation and the use of Albunex. These patients were studied before hysterectomy to confirm that there were no tissue effects.

There have 5 phase 3 trials; 164 women that have received Albunex in these trials. In Europe a total of 205 were studied in Sweden and 43 were studied in France. These patients were not compared with laparoscopic evaluation, and therefore are evaluated only for safety. These patients were evaluated some for safety only, and 309 actually received Albunex; 2 did not meet the criteria.

So of these patients, the total enrolled for study have been 433; 309 have received Albunex, 275 have underwent

HSG. HSG as a screening test is not considered the gold standard for tubal patency, and therefore, we will discuss the patients that underwent the sono-HSG with Albunex and laparoscopy.

In the United States there were 10 investigative sites, and these sites enrolled between 7 and 30 patients, and therefore there is cumulatively less experience with this technique I would say, in the investigators in the United States compared with the group in Sweden, where 2 investigators each enrolled 100 patients each, and used Albunex in at least 50 of them each.

The French study again, will not be really considered, since they didn't do laparoscopy.

The objectives of the phase 3 studies were to determine the safety, the tolerance to patients during the procedure and the efficacy of this agent for determining tubal patency.

We consider the positive results to be demonstration of patency, because this is a screening test for patency, and therefore sensitivity will represent the detection of a normal tube as determination of patency.

Specificity will refer to the detection of an abnormal tube or tubal occlusion.

These patients were all similar in their age range. They were all women in reproductive years, and of fairly normal height and weight.

The race of the participants reflected the racial distribution in the clinical centers in which they were studied.

We studied tolerance in the United States in a carefully designed protocol to elicit acute effects. Every patient received a baseline ultrasound, a very important part of the examination, to evaluate the morphology of tubes and the ovaries and the uterus.

Then the cervical catheter was placed with a balloon inflated with saline. Then tolerance was evaluated with saline instillation, and then separately when Albunex was instilled. Then later, sometimes immediately afterwards or often within a day or two, when they underwent the hysterosalpingogram.

You can see that mild discomfort, as happens anytime you instrument the uterus was comparable between

instillation of various agents, as was moderate and severe discomfort or pain.

There were 62 patients that experienced 85 adverse events in the entire population. The adverse events consisted of discomfort and pain primarily. As I said, instrumenting the uterus is not a particularly pleasant procedure. Analgesics were given on determination by the clinician.

The accuracy of this technique was evaluated in 213 tubes that underwent both laparoscopy and the Albunex sono-HSG. The findings were that the sensitivity for tubal patency with combining all the studies in Sweden and the United States was 87 percent, and the specificity for tubal disease was 40 percent. This is comparable to the current screening study ranges, which are very wide for sensitivity and specificity in the literature.

The confidence interval is fairly good for sensitivity and specificity is rather broad. Some of the reasons for the low specificity include investigator experience with this technique and with this agent. We learned some things about it as this trial went along, and

the fact that tubal spasm can be transient, and cause an appearance of obstruction that is false.

In conclusion, we found that Albunex is a safe and convenient, and importantly office-based procedure that allows us to add the determination of tubal patency to a standard ultrasound screening exam, which all women undergoing fertility already receive.

So with a timed ultrasound and the use of no radiation to the gonads, no iodinated contrast, we can evaluate the tubal patency, the ovarian morphology, the follicular response, endometrial response to treatment during a normal cycle, and the uterine morphology all in one combined test, which is an advantage, we believe, to the patient.

The fact that the treating physician may do this easily in their office, and thereby elicit more information from a single exam than they may from an exam done elsewhere by another physician, and it saves time and effort for the patient, undergoing one, instead of two exams.

I'm going to turn this discussion back over the Jennifer Kettner. Thank you, very much for your attention.

DR. KETTNER: Based on what we have presented here today, we believe we have the data that demonstrates that Albunex is a safe and efficacious product that is indicated for use with transvaginal ultrasound to assess fallopian tube patency.

Thank you.

DR. HALBERG: Thank you.

Since we're ahead of schedule, instead of taking a coffee break, we'll have the FDA do their presentation first.

While we're waiting, maybe I can ask the presenters if you have any data at all on subsequent reproductive outcomes after your sono-hystero-grams, specifically spontaneous abortions and ectopic pregnancies?

DR. PARSONS: That wasn't collected in the studies, but I can tell you from the 30 patients I did in the phase 2 study, out of those 30 patients there were 4 pregnancies the following cycle. I think that's all I can contribute. There is one ectopic pregnancy several cycles later, after cannulation of the tubes, which probably wasn't relevant.

DR. HALBERG: Thank you. Mr. John Monahan is the FDA's lead reviewer for PMA 900059 Supplement 4, and will present an overview of the PMA from the FDA's perspective.

Agenda Item: FDA Presentations, PMA Overview -
John Monahan

MR. MONAHAN: I would like to begin my presentation this morning by simply acknowledging the people who worked on this application. They put a lot of work in. We had Dr. Cherska(?), Sachs, and Schultz who did a clinical review. Dr. Malsant(?) was our toxicologist who reviewed the studies dealing with toxicology and irritation; Mr. Gary Kamer, who did the statistical review of all the data, and myself, who did a general review.

Because of the nature of this particular panel and the application for this device, we decided to use two outside reviewers who were experts in the OB/GYN area. We asked Dr. Sandra Carson to review the material, and she will be our lead reviewer today following the FDA presentation.

We also had Dr. Michael Diamond review the clinical data for this. Dr. Diamond is a member of the OB/GYN panel. Dr. Carson is a consultant to that panel.

As has already been mentioned, Albunex was approved CDRH and FDA on August 5, 1994. At that time it was approved as an aid for ultrasound contrast enhancement of ventricular chambers, and improvement of endocardial border definition in patients with suboptimal echoes, who were undergoing ventricular functional and regional wall motion studies.

To date, the sales of this agent have been more than 25,000 units in the United States, and greater than 30,000 units overseas. So there has been some extensive experience with the product used in people.

The submission before the panel today is for a new indication for use for Albunex. As the sponsor has previously mentioned, it is for use with transvaginal ultrasound to assess fallopian tube patency. At the present time, there are two alternative procedures in use, hysterosalpingography, which requires radiographic imaging, and an x-ray contrast agent to visualize a cervical canal, the uterine cavity and the fallopian tubes.

The other technique is diagnostic laparoscopy, which is of course, an invasive surgical procedure that is

normally performed in the hospital, under general anesthesia, with the associated risks. This procedure uses instillation of a dye into the uterus in tubes to assess the tubal patency by visualization of spillage into the peritoneal cavity.

In the original PMA approval for Albunex, the company did a number of studies dealing with the toxicology, teratology. They did a number of irritation studies, mutagenicity and immunology. These were mentioned by Dr. Wible.

The present submission included two additional studies which have been described to you. That is, the rabbit irritation study and the rat irritation study in which no adverse effects were associated with the instillation of the Albunex.

Currently, we have asked the company to do a biodistribution study; because of the different route of administration, we felt that since this was not an IV administration, that we needed to take a look at this.

The study was designed to determine the pharmacokinetic and biodistribution characteristics of

radio-labeled Albunex injected into the peritoneal cavity of female rats. We recognize that this is not the normal route of administration for this agent, however, if it had been instilled into the uterus, there would have been leakage, and it would have gotten on the animal's fur and confused the results. So we felt that it was more appropriate to have the agent injected into the peritoneal cavity of the rat.

The dose volume being used in this study is 0.66 milliliters per kilogram, and this represents a worst case scenario, since it assumes that the entire maximum clinical dose for a 45 kilogram subject would enter the peritoneal cavity, and in practice that is probably not true.

The organ test time for this particular study will range from 0 out to 72 hours. The agency wants to see the results of this test before making any final determination on the product. That should not influence your deliberation today.

At this point, I would like to turn the podium over to Dr. Daniel Schultz, who will discuss the clinical evidence.

Agenda Item: Clinical Studies - Daniel Schultz,
M.D.

DR. SCHULTZ: Good morning, Dr. Halberg, members of the panel. My name is Dan Schultz, and I will be discussing the clinical studies associated with Supplement 4 of this PMA, "Albunex for Fallopian Tube Patency."

We believe that this agent has the potential for having a significant public health impact. Infertility is a major problem in this country, and is one which is actually increasing due to the prevalence of sexually transmitted disease, the preference of many couples for delayed childbearing, and other factors as well.

As has been already said, fallopian tube disease accounts for somewhere between 25 and 50 percent of all infertility, and as has also been said, the current diagnostic modalities, both individually and in combination have less than ideal efficacy.

The indication as proposed for this supplement has been talked about previously as indicated for use with transvaginal ultrasound to assess fallopian tube patency.

As has also been discussed, a number of clinical

studies have been performed in this country, as well as in Sweden and France. We felt that in looking at these studies, that they were designed both to talk about feasibility dosing, and ultimately to assess safety and efficacy.

One of the things that we look at very carefully when assessing multiple studies, and especially those done both foreign and domestic is to examine the comparability of those studies. We felt that in looking at the objectives of the studies, that they were essentially identical, that is, to determine safety, tolerance and effectiveness of Albunex enhanced ultrasound for assessing fallopian tube patency.

In terms of the demographics, as has previously been mentioned -- and I apologize, this is a busy slide, which was taken right out of the PMA -- we felt that the demographics was similar with the exception of the fact that the United States studies obviously contained a wider range of racial mix, as would be consistent with the populations in the United States and abroad.

In terms of the methodology, all of the phase 3 studies were masked with respect to the results of the

Albunex study and the comparative study, whether it be HSG or laparoscopy. The inclusion/exclusion criteria were similar for all the different studies. The dose ranges were similar, as can be seen in this slide.

Perhaps of most significance is the fact that the endpoints in the studies were somewhat different. We did believe, however, in looking at those endpoints that there was a good reason why the endpoints were different, namely that no definitive gold standard exists for the diagnosis of fallopian tube disease. The United States studies were designed primarily to demonstrate concordance with hysterosalpingography, whereas the Swedish studies were designed primarily to compare HHS and HSG.

In looking at the results of the studies, what we found was essentially a very low incidence of adverse events. There was no mortality associated with any of the studies. There were no serious adverse events associated with any of the studies.

There was no clear evidence of adverse events being device related, however, one of the shortcomings was that the safety data was not concurrently controlled, but

rather was historically controlled, and therefore it is somewhat difficult to compare the results of adverse events comparing the HSS with the HSG.

This was partially explainable by the fact that the studies were performed within a short period of time, and it was difficult to separate the effects of one study from another study.

Another shortcoming, which has already been alluded to is the fact that the safety data only was followed out to 24 hours. So that we don't have as much data as we might like for potential long range effects.

In terms of the effectiveness, as has been previously mentioned, sensitivity, which was defined as a determination of patency, and specificity, which was defined as a determination of blockage. Within the number of studies that were performed, essentially all of the data was consistent with a sensitivity range of between 80 and 90 percent, and specificity of 40 to 50 percent. As I mentioned, one of the things that we looked very carefully at was the consistency of the data between the various studies.

Again, this is the safety data which was presented by the sponsor in a different format. As you can see, by far the largest percentage of adverse events was with respect to pain and cramping. If you compare this both to the saline and to hysterosalpingography, this number looks pretty good.

Again, as I mentioned earlier, efficacy was compared to both in the United States and in Europe to looking at the efficacy of hysterosonosalpingography and hysterosalpingography comparing hysterosonosalpingography to laparoscopy or HSG, and the sensitivity or patency rate was 83.7 percent. The specificity or determination of the accuracy in determining blockage for the United States study was 55 percent; 88 percent and 44 percent for the European studies.

In another way of looking at the data, the HHS was compared to laparoscopy, as opposed to HSG being compared to laparoscopy. Again, as I mentioned previously, what we found somewhat encouraging was the fact that the data for the HHS was extremely consistent in this comparison; the sensitivity was 87 percent and 40 percent.

One of the things that you will be looking at in terms of the questions that we are going to be asking the panel is the fact that the indication for use has been revised, both with the concurrence of the agency and the sponsor. I would just like to talk about that for one second.

Originally the indication included an indication for assessment of pelvic organs. We actually concurred with the sponsor in their conclusion, based on this and other data presented in the PMA that there were no clear differences in agreement between Albunex or saline, and baseline scan or laparoscopy. Thus, we did not feel that the sponsor had demonstrated an enhanced effect of Albunex in looking at pelvic organs, and therefore the more limited indication for fallopian tube patency was decided upon.

With that, I would like to thank you. We will be asking you to look at several specific questions regarding the safety, efficacy and clinical utility of this device, and also be asking for your help in terms of determining the optimal labeling for this device.

I thank you very much.

DR. HALBERG: Thank you, Dr. Schultz. Mr. Monahan?

Agenda Item: General Issues - John Monahan

MR. MONAHAN: At this time, what I would like to do is put up for the audience, the issues that we would like the panel to focus their discussion on. By no means are we attempting to limit your discussions to simply these issues, but merely to point out some of the things that we feel should be discussed by the panel.

The labeling originally proposed by the sponsor included the following indication for use statement as indicated by Dr. Schultz. "Albunex is indicated for use with ultrasound assessment of the female reproductive organs. Albunex demonstrates fallopian tube patency when used with transvaginal ultrasound."

The revised indication now states that Albunex is indicated for use with transvaginal ultrasound to assess fallopian tube patency. We would like the panel to indicate whether they believe the revised version of the indication for use statement is appropriate, and is justified by the data provided in the PMA.

Do you believe that the PMA has adequately demonstrated the safety of the device, and that the contraindications, warnings, precautions section of the label is adequate with respect to:

(1) Whether residual albumin in the fallopian tube or uterus could lead to tubal occlusion or other fertility-related problems?

(2) Whether residual albumin in the fallopian tube or abdominal cavity could increase the risk of PID in patients with no prior history of PID, with a history of PID, or with active infection?

(3) We also ask whether there are any other safety concerns. Given that many different data analyses were used to demonstrate effectiveness, we ask the panel to offer some guidance as to the most appropriate way to present this data in the labeling. This section of the labeling should offer the user a clear and accurate assessment regarding reliability of the clinical information provided for this device.

(4) If approved for the new intended use, this device would, in many instances, be used in an office

setting, as opposed to a hospital or freestanding radiological suite. Does this raise any special safety concerns?

(5) The fifth issue is use of the device, which combines a technique of diagnostic ultrasonography with those of hysterosalpingography would be used by physicians with varying degrees of experience with each of these modalities. Do you believe that the instructions for use in the current labeling are adequate, or should the labeling include additional written instructions, or are other training methods needed for the physicians?

(6) After reviewing the information provided by the sponsor, including the clinical and pre-clinical data, do you have any other recommendations for changes to the labeling of this device?

(7) This is the critical question I believe, has the evidence provided by the sponsor in the PMA adequately demonstrated the safety and effectiveness of the device when used for its intended purposes?

(8) Finally, does the panel feel that there are any issues or concerns regarding the safety and/or

effectiveness of the device that have not been completely resolved by the data in the PMA, and should be addressed through a long-term or post-approval study or studies?

At this time, I would also like to note for the record that the material passed out by the sponsor to the panel members has previously been submitted to the agency, and was available for review. It is simply a copy of the slides that they presented during their talks.

Thank you.

DR. HALBERG: Thank you. At this time let's take a 20 minute coffee break, and come back at 10:00 a.m.

[Brief recess.]

DR. HALBERG: I'd like to bring the meeting back to order. Before we proceed with the discussion of PMA P900059 Supplement 4, Mr. Monahan will remind panel members of their responsibilities in reviewing today's supplement to the pre-market approval application for Albunex.

MR. MONAHAN: The Medical Device Amendment to the Food, Drug and Cosmetic Act enabled FDA to obtain a recommendation from an outside expert advisory panel on medical device PMAs which are filed with the FDA. We are

asking you to make a recommendation concerning whether this PMA supplement should be found approvable, approvable with conditions, or not approvable.

A recommendation must be supported by data in that application, or by publicly available information. Your recommendation may take one of three forms:

(1) You may recommend that the PMA supplement be approved with no conditions attached to the approval.

(2) You can recommend that the PMA supplement be found approvable, subject to specified conditions such as resolution of clearly identified deficiencies cited by you or by FDA staff. Examples can include: resolution of questions concerning some of the data or changes in the draft labeling. You may conclude that post-approval requirements should be imposed as a condition of approval. These conditions may include a continuing evaluation of the device, and submission of periodic reports.

If you believe such requirements are necessary, your recommendation must address the following points: the reason or purpose of the requirement; the number of patients being evaluated; and the reports required to be submitted.

(3) You may also find the application not approvable. The Act, Section 515(b)2, Sections A-E, states that a PMA can be denied approval for any of five reasons. I'll briefly remind you of three of these reasons that are applicable to your deliberations and decision. The three are:

(1) There is a lack of showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the labeling. To clarify the definition of safe, there is a reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence that the probable benefit to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use outweigh the probable risks.

The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

(2) The PMA may also be denied approval if there

is a lack of showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling.

A definition of effectiveness is as follows:

there is a reasonable assurance that a device is effective when it can be determined based upon valid scientific evidence that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use will provide clinically significant results.

(3) The PMA may be denied approval if, based on a fair evaluation of all the material facts, the proposed labeling is false or misleading. If you make a non-approvable recommendation for any of these stated reasons, we request that you identify the measures that you believe are necessary, or steps which should be undertaken to place the application in an approvable form. This may include further research.

I would like to turn the meeting back to Dr. Halberg at this point.

DR. HALBERG: I would just like to remind public observers at the meeting that while this portion of the meeting is open to public observation, public attendees may not participate unless specifically requested to do so by the panel.

I will now turn the discussion over to Dr. Carson.

Agenda Item: Panel Discussion, Recommendations and Vote - Sandra Carson, M.D., Discussion Leader

DR. CARSON: Thank you.

Let me begin by commending MBI and Mallinckrodt, as well as FDA for providing very lucid and clear materials in both the PMA and the materials we have in front of us today. It really helps as a reviewer to have it presented so nicely, so thank you.

Before we begin formal discussion of the questions, could I ask the panel if they have any discussion for either the experts that Mallinckrodt brought today, or FDA itself?

I do have a few questions. Perhaps, Dr. Kettner,

you can decide who to answer this. One, I wanted to know if you can warm the substance to body temperature, if there are any adverse effects to the device prior to use?

PARTICIPANT: Could you define the term "adverse effect?" I would like to see where you are going specifically with the question.

DR. CARSON: Well, I would like to know can you device to 37 degrees prior to instillation?

PARTICIPANT: There would be no problem with doing that. There would be no expansion of the significance in the microspheres if that was done to it.

DR. CARSON: So then it can be used at body temperature?

PARTICIPANT: Certainly.

DR. CARSON: The second point, I think to Dr. Parsons. In your presentation of the actual procedure you didn't mention saline flush after device use. Is that part of the protocol, or could you comment on that?

DR. PARSONS: That was an option. The reason I use saline following the Albunex is simply as a chaser to extend the effect of Albunex after infusion. It wasn't part

of the protocol, it was just an optional maneuver.

DR. CARSON: Is this going to be a recommendation by the company for device use, to follow it with a saline flush?

DR. KETTNER: Yes, it will be.

DR. CARSON: There will there be a volume recommended?

DR. KETTNER: There will be a range recommended.

DR. CARSON: Did I miss that in the labeling?

DR. PARSONS: No. There's been some discussion about that.

DR. DESTOUET: I have a couple of questions for Dr. Parsons. Following the Albunex HSS and demonstration of bilateral tube obstruction, what is the next step in the infertility work up?

DR. PARSONS: That is really up to the practitioner and up to the observation of the obstruction. In studies done using HSGs, which are really the data we have to go on, one study of 750 HSGs indicated that in people that had tubal obstruction, there was an 89 percent chance of severe peritoneal or tubal disease at laparoscopy.

In people that had proximal obstruction, not distal obstruction, but just proximal obstruction, where there was no dye going down the tube at all, so it is a sort of a suspicious reading and it could be due to spasm, there is 50-50 proposition whether or not you find severe tubal damage at surgery. In people that had apparently patent tubes, there is a very low percentage.

So now with IVF, a person with evidence of bilateral obstruction where the tube is obstructed distally, many people would immediately send them to IVF without further evaluation, since this is a fairly reliable observation. Whereas with proximal obstruction, I think we are now devising ways to overcome the inherent difficulties of this test to give us false positives when it comes to proximal obstruction.

We sometimes cannulate the tube immediately, which is possible using this technique right in the office, and then using the contrast to show that the tube is now patent. Or we will do another study, whether it's a laparoscopy or some other evaluation.

So I think it really depends on the -- as this

technique gets put into more use, I think the triage pathways will be developed by clinicians using it. Anybody using HSG now has a variety of ways to go, depending on the findings.

DR. DESTOUET: Part of my concern is that given the specificity of 40 percent that you have identified overall in the study, how many women will undergo unnecessary laparoscopy because of a false positive test, or a test indicating corneal obstruction, when really there may be spasm or something?

Do you anticipate that as the algorithm plays out, that there will be some women going from the Albunex HSS to the regular HSG, hysterosalpingography, and not automatically to laparoscopy?

DR. PARSONS: As I said, right now we have the technology to prove patency in the office if there apparent corneal obstruction. I would personally be disappointed to see a patient go immediately to laparoscopy, or even to the other screening exam, which has the same problems as this one. We are devising ways to deal with that. One is immediate cannulation with a small tube.

Another is to do it at a time in the cycle when the hormones are different, and the tube is more relaxed and less likely to spasm, which is the luteal phase. So that is in development.

DR. DESTOUET: How difficult is it to cannulate the fallopian tube? Can most gynecologists in an office-based practice, and whom we anticipate that this will be used by do that that procedure, or would that patient be referred to a medical center for instance?

DR. PARSONS: This test requires experience and understanding of what it is about. It really can't be done I believe, by a person that isn't a very experienced sonologist or sonography. I think that the radiologists that are interested in reproductive imaging will certainly do this test, because not every office setting, whether it is an infertility specialist or anybody else, is capable of using it.

I think that whoever is doing this will probably have the capability of cannulating the tube. It is not particularly different. The uterus is made to slide everything into the tube. It is designed that. I do think

it is a test that is going to take experience and training to gain wide use. I don't think it is going to take the country by storm. HSG has a very strong position now.

DR. DESTOUET: Where in the algorithm of the work up of the infertile woman does hysterosalpingography occur? Is it very early in the procedure or late in the work up?

DR. PARSONS: It depends on what the patient presents with. I think Dr. Carson can answer this as well as I can, because if a person presents with abnormal cycles, no bleeding, no periods, first we try to make them ovulate before going on to evaluate the tubes, because we do the simple things and the obvious things first.

A person who has a history of ovulatory infertility, with no pregnancy despite regular menses and exposure to sperm deserves a remediate evaluation of the tubes.

DR. DESTOUET: So when you say it's not going to take the country by storm, you mean this will generally not be the very first test that gynecologists will provide?

DR. PARSONS: What I mean is this technique for screening tubes will require training on the part of people

that use it. I would, as a commercial for my own subspecialty say that reproductive endocrinologists are the most experienced at ultrasound of the reproductive tract in gynecology. So we can assume that most of them will be capable of it, but it will take time.

What we have found is that it takes probably 20 procedures for people to get really used to finding what they seek.

DR. CARSON: Let me just comment in answer to your question. The American Society of Reproductive Medicine, in their technical guidelines, has recommended that any imaging diagnosis of blocked fallopian tubes be substantiated and confirmed by another procedure.

DR. CHOYKE: I have a question for one of the company representatives about whether any animal reproduction studies were done after administration of Albunex?

DR. WIBLE: Reproductive studies that were done, were done in conjunction with IV administration of Albunex, and in conjunction with the teratology studies that I presented earlier. In that study, the administration of

Albunex did not have any teratogenic effects.

DR. CHOYKE: So nothing was administered by the uterus?

DR. WIBLE: No.

DR. ALAZRAKI: One other question. We have information about the race profiles of the participants in the study. Are there data on the history of PID or no history of PID, or active PID on the participants? Is that data available?

DR. PARSONS: There's historical data available. They are excluded from the study if there is suspicion of active infection. So any person entered into the study was clinically found not to have any infection.

DR. ALAZRAKI: Do we know what percentage then of the women in the study had a history of PID?

DR. PARSONS: I imagine we do, but I don't.

DR. ALAZRAKI: Okay.

DR. R. LERNER: I have a question about the efficacy compared to saline of the Albunex. If the endpoint is spill in the peritoneal cavity, how does Albunex compare to saline or perhaps some agitated solution that is

injected?

DR. PARSONS: That is a good question. Saline is a very accurate indicator of patency of at least one tube, which you which it accumulate in cul de sac. It has an accuracy of about 95 percent, but you don't know which tube is patent. The importance of this contrast agent is to show us details of which tube is patent, and whether or not -- in my opinion it is important to see whether or not there is contact between what is emanating out of the tube and the ovary. Saline is a very good method of indicating one tube being patent.

DR. R. LERNER: The second part of the question then is what about agitated saline or something that would introduce microbubbles?

DR. PARSONS: Oh, I have tried everything. That is why I was so excited to finally have a consistent method of imaging the tube. Around the world right now air is used, and just half syringe of air is just injected right into the uterus. I don't find that as satisfactory, but there are other methods, they just aren't as reliable. They aren't stable enough.

I actually tried sonicating albumin in my office with a sterile hood, and it wasn't stable enough.

DR. R. LERNER: The third part of the question is how important is it to find bilateral versus unilateral spill, or to identify one blocked tube versus two?

DR. PARSONS: Oh, it's very important. As I said, we do the simple things first. If a patient has an operating ovary and a patent tube, and contact between that tube and ovary, one can observe ovulation and allow her to try and conceive on her own. Whereas with both tubes blocked, one is forced to intervene promptly.

DR. CARSON: Any other questions from the panel? Do we have enough to proceed? Let's go to the first question.

The labeling originally proposed by the sponsor is indicated on the slide. This has been changed based on review to the labeling, "Albunex is indicated for use with transvaginal ultrasound to assess fallopian tube patency." Do you believe that this version is appropriate as justified by the data provided for us today?

Any comments from the panel?

DR. CHOYKE: Well, I'll open with my concerns about the label, and that is that some of the tables that were presented -- specifically on page 43 -- show that even in cases where both tubes were blocked, the Albunex could only make that diagnosis in about half of them, and that in fact in 4 of the 14 patients, Albunex studies showed both of those tubes were patent. In fact, that is on 43 and 45.

I'm concerned that this is a test to identify tubes that are blocked, rather than tubes that are patent, and that in the extreme case of bilateral blockage, which is very important I think, the test wasn't able to do very well. In fact, it called 4 out of the 14 both patent, not to mention all the disagreements between left and right, which side is patent.

So I just want to voice my concern about what I call this false positive rate, although the labeling here in the document is a false negative rate.

DR. PARSONS: Now of course those patients would end up being confirmed most likely by laparoscopy. So if you have --

DR. CHOYKE: Either the test would say that they

are bilaterally patent, and they wouldn't go on necessarily to another test. Yet, they might go into another algorithm in terms of their infertility work up with the thought that they had patent tubes, and that would be completely misleading.

DR. PARSONS: Can I speak to that? Two of those tubes were in my study group. The fact is that they were verified as being patent or not patent by laparoscopy. Laparoscopy, if you will notice in the Swedish data, there were three uncertain laparoscopies. They weren't sure even at laparoscopy if a tube was patent or not.

In the United States we tended to avoid uncertain diagnoses, and we said yes or no. In my case, in this particular patient's case, her tubes were patent both by HSG and by this technique, and at laparoscopy, because of some malplacement of the catheter or other, the tubes looked completely normal, but no dye could be put through them. This is observed that up to 5 percent of false positives for obstruction diagnoses can be made a laparoscopy.

So I think that one of the problems with evaluating these data is that there are no gold standards.

DR. CHOYKE: I only have to say that we have to have some gold standard here to assess. Otherwise, we are just saying whatever agent that does whatever is fine. So the gold standards that were selected here were HSG and laparoscopy. I think we have to go by them. That's just my opinion. So I just wanted to get that out on the table early.

DR. CARSON: Thank you for bringing that up.

Can we have just an idea of panel consensus as to whether the revised version of the indication is appropriate as justified by the data? Can I see a show of hands for those who think that it is? And those that think that it is not?

[Whereupon there was a show of hands, six affirmative, one no vote.]

DR. ALAZRAKI: I just want to clarify that I think that it is, relative to the previous indication, which has been revised, and that indeed is what the focus of all of these studies, is the fallopian tubes, and not any other anatomy.

DR. CARSON: Thank you.

Do you believe that the PMA has adequately demonstrated the safety of the device, and that the contraindications, warning, precautions section of the label is adequate with respect to first, whether residual albumin in the fallopian or uterus could lead to tubal occlusion or other fertility-related problems?

So the question here is if the labeling, as we mentioned, does not require a saline flush post-administration, would there be any concerns about the risk of the device staying in the tube, and possibly leading to subsequent occlusion?

DR. CHOYKE: Well, I think the animal studies showed that there wasn't really any irritative effect of the agent. It seems to me that the basic test -- a basic test, not the basic test would be how animals reproduced after this agent was given. This is an infertility setting, and certainly we ask that of other drugs where it isn't in the infertility setting.

You would want to know that animals reproduce normally after this has been spilled in the manner that it is intended to. So I think there is, to my mind, a missing

piece. I don't know that that should hold up approval of it, but it should be supplied at some point.

DR. DESTOUET: As I read the protocol, it seemed as though the patients all had a saline flush following the Albunex study. Am I incorrect?

DR. PARSONS: No, they didn't all. The option was there, and it was collected if it was done, but that wasn't the routine.

DR. DESTOUET: Do we know in which percentage of patients there was a flush, and which percentage of patients had no flush? If so, was there a difference in the outcome regarding any morbidity in those women?

DR. PARSONS: I don't see the point of that, to be honest with you.

DR. DESTOUET: Well, did any women who have Albunex left in their fallopian have any increased problems, whether it is pain or fever or any increased morbidity?

DR. PARSONS: As I tried to show, but it was a very short videotape, the Albunex has a very short live, which is what is good about it, because it doesn't obscure the picture by accumulation. In a hydrosalpinx for

instance, you can watch the contrast agent diminish to saline, which is its stillulant(?).

These become submicron sized residual pieces of albumin -- submicron size, mind you, less than the size of a red cell -- when the microsphere has lost its gas. So you can watch that happen as you are observing, so there is no intact microspheres left within a few minutes of infusing this in an occluded tube.

If you insert it into the tube, and you watch it run down the tube into the peritoneal fluid, that is an even faster demise for these tiny microspheres. In albumin we are dealing with a system that is constantly contracting. Anything that is put into the uterus or the tube is immediately expelled in one direction or another into the peritoneal cavity, or into the vagina.

I have actually done these studies putting Albunex at the surface of the cervix, and watching it go up through the uterus very quickly. We know that sperm are within the peritoneal cavity within 15 minutes. So I think it's highly unlikely that there is going to be much in the way of these tiny particles left behind for very long, and albumin is an

indigenous substance.

You can't really do these studies in animals, because human albumin is antigenic to animals.

DR. HACKNEY: Along those lines, I'm not sure we want to get too hung up on the issue of a saline flush, because the question would be would a saline flush be effective to prevent whatever it is we think might happen if the albumin were left in there, and one would need to show that it actually worked.

To address that question, one could ask what was the follow-up of these women in terms of reproductive success later? Is there any evidence that the Albunex had any effect on them? That, I think, would answer the question that everyone is worried about more than another technical detail of unknown effectiveness.

Do we have any data -- we know who these patients were. What happened to them in the months thereafter? Did they conceive at a higher or lower rate than one might have expected otherwise? Was there a higher rate of reproductive difficulties?

DR. PARSONS: Hysterosalpingography has been

described as increasing pregnancy rates following its performance using lipid contrast agents. Lipid agents we know cause fairlomas(?) in the peritoneal cavity, coat the tube, at least temporarily, and are irritating to tissues.

The other agent that is used is a water-based water soluble contrast which is irritating to tissue as well based on tissue studies. This does not enhance pregnancy rates apparently.

All we have with Albunex or saline or any other flush are anecdotal experience. As I said, four patients that I took care, conceived within the following two cycles. Since there are a lot of interventions done on these patients, it is very difficult to compare pregnancy rates. You would almost have to compare normal women with normal women, and that is a difficult study to pull off.

DR. HACKNEY: I guess I was wondering if there is more data on the other patients besides the 30 that you did?

DR. PARSONS: No, that was not collected. I'm sorry, that wasn't the focus of this.

DR. CHOYKE: A problem with that is that they got HSGs or laparoscopy, so they got a lot of interventions. So

you can't really -- if they just had, as indicated the Albunex, fine, but this is not useful. That's the problem.

DR. CARSON: Do you believe that there is enough information to decide on whether the residual albumin can cause fertility-related problems? Could we just show a brief show of hands from the panel? Those who think there is enough documented, please raise your hand? Those who think there is not enough?

[Whereupon there was a show of hands, all indicating no to the question.]

DR. HACKNEY: I wouldn't make it quite as narrow as whether it is the residual albumin in the fallopian tube. My point is that we don't really know whether something untoward happened to these women in their reproductive abilities after it, whether it is due to residual albumin in the fallopian tube. I think there was a good argument made that it probably would not be residual albumin sitting in the fallopian tube for any substantial period of time, but we still don't know what happened to them.

DR. CARSON: I think that this brings up a good point, and probably all of our concerns. Let me bring up

for discussion, do you think that this could be handled -- as we look at the labeling and approve or disapprove -- do you think it could be handled by asking for some post-marketing surveillance as to subsequent pregnancy after such tests?

MR. MONAHAN: Excuse, Dr. Carson, if I could interrupt for just a moment?

The people in the other room cannot see a show of hands on the TV camera. So if we could simply have a count of those saying yes or no, that would be helpful to the people outside.

DR. CARSON: Okay. Did somebody count the first question? Six yes and one no. Then the second question, Part A was I believe all no.

DR. KETTNER: Could we add an additional comment to the question of the albumin.

DR. J. LERNER: I'm Dr. Jodi Lerner. I'm Assistant Professor of OB/GYN at Columbia Presbyterian in New York. I think I'm supposed to say that my time today and my expenses were paid by Mallinckrodt, and I was one of the investigators with Dr. Parsons on the study.

I just wanted to tell you a little bit about how our protocol went. I placed the balloon catheter in. I did the sono-HSG, finished the study, and then with the catheter still in, the patient went straight down to the hysterosalpingogram suite.

So one of the questions that we'll come to later on that I can make a comment about, about the follow-up, and the concurrent and separating the adverse events. Part of the problem is still with this problem that they followed immediately with the hysterosalpingography, so I don't know that we can ever really separate post-procedure to be separated out for the sono-HSG versus the HSG afterwards.

DR. CARSON: Thank you, Dr. Lerner.

I think if it comes to the panel's decision as to whether you can think that this issue can be handled by requesting some post-marketing surveillance? Comments?

DR. ALAZRAKI: The problem remains that these women have so many other procedures done, that how we could separate out what was caused by or what could be attributed to any albumin product in the fallopian tubes, I don't see how.

I would just like to also make a comment about the residual albumin product. We know from other data in injecting particles like these that the albumin particles are removed by a combination of macrophage and enzymatic breakdown of the albumin. At least in the lungs for example, the half life in the lungs is something between 3 and 12 hours.

Now there may not be the same access, or there may be in the fallopian tubes to macrophages and enzymatic effects as in the lungs, but I would presume that the albumin doesn't stay there forever; probably no more than a matter of hours, to a maximum of a day.

DR. DESTOUET: I think that it's important to know with post-PMA data the ectopic pregnancy rate; some of the things that one would normally assess with this type of procedure. I think it is something that the FDA would certainly want to know following the initiation of this test as well.

DR. CHOYKE: With regard to your question, I would rather not answer this individual question now, but in the context of question 7, when we have everything out on the

table.

DR. CARSON: Okay, we'll do that. Thank you.

Then B and C were essentially the same comment with pelvic inflammatory disease and other safety concerns that we have. I think we have probably addressed this in our previous discussion with this, unless you had specific comments.

DR. HALBERG: I would like to make a comment on that. Right now the labeling reads, "Patients with current gynecologic infection should be treated with antibiotic and the procedure possibly delayed until resolution of the infection." Since no patients in the studies had pelvic inflammatory disease, we may want to just delete the word "possibly," so the sentence would read, patients with current gynecologic infection should be treated with antibiotics, and the procedure delayed until resolution of the infection, because there is nothing urgent about this procedure.

DR. PARSONS: I think that was to cover the idea that if somebody found vaginitis, they would treat that, but that has no direct bearing on the tubes. Gynecologic

infection is a fairly broad term. So I agree completely with the idea of deleting "possibly." I think we have to be careful.

DR. HALBERG: I think that might address some of the PID concerns.

DR. CARSON: Let's move on to question 3. Given that many different data analyses were used to demonstrate effectiveness, please offer some guidance as to the most appropriate way to present this data in labeling. This section of the labeling should offer the user a clear and accurate assessment regarding reliability of the clinical information provided for this device.

Let me just point out that on pages 45-47 give tables of sensitivity, specificity and predictive values. Perhaps the panel might look at these in their consideration.

DR. HALBERG: Could I ask if there is an FDA statistician who may be able to address this from the FDA perspective in terms of putting these numerous tables together so that they can be easily viewed by people using the product?

DR. CARSON: We basically would like some guidance as to how to present the efficacy data in the labeling so that the user has a good idea of the efficacy of the device.

MR. KAMER: I'll start with FDA statisticians usually do not get involved with labeling issues. That is not an area for us. That is more of a clinical issue. Are you talking about now the fact that you have different studies?

DR. CARSON: There are a number of sites in the material given to us, and some did the procedure a bit differently, and we have an overall per tube, as well as per patient sensitivity and specificity. How could we present all of this data to give the user a good idea as to what to really --

MR. KAMER: It's going to be difficult simply because -- I'm not sure it can be done -- I did make some comments in my reviews concerning the poolability of the data, although it may be justified to pool the data, there were different protocols used. You had some differences in the studies; the endpoints, the methods which it was being compared against, et cetera. I don't think there is any

statistical answers to it. This is the type of thing that you had to work out.

I did not get an answer as such, of the poolability of the data. Again, it may be totally poolable, but I did not see that. If I'm not convinced of the poolability, I'm not sure you can put it into one number or a set of numbers across sites, across studies.

DR. HALBERG: Is it up to the FDA to include all those tables?

MR. KAMER: Somebody who is the FDA may have to replay to that. Again, that's not a statistical issue, but it would be -- any single number may not be -- if these were poolable, if they had been shown to be poolable sites, poolable studies and been under the same protocol, any number would still be an estimate, an average. There would not be a precise number that is applicable to any one site, any one population.

We don't have even that with us. It's very difficult. If we make the labeling so long, it makes it very difficult to understand also. That is an alternative. How long it should be? I don't know how detailed.

DR. CARSON: Dr. Smathers, did you have a comment?

DR. SMATHERS: Well, in the previous summary from the FDA this morning, sensitivity was defined as the determination of patency, and it is given about 80 to 90 percent, which I assume was a pooled number. Then specificity was defined as the determination of blockage given the 40 to 50 percent.

Are those still valid numbers?

MR. KAMER: That's a range. It's not from one site?

DR. SMATHERS: The realistic --

MR. KAMER: A range is one way of doing it.

DR. SMATHERS: It's a realistic presentation. I guess the question is, is the specificity really defined as the accurate determination of blockage? Or maybe I'm asking, what do you mean by specificity?

MR. KAMER: Here you do not have a good standard, so you are dealing with something a little bit different than if you have a gold standard, and you know that you are right or wrong. That would be the way specificity would be defined, from my understanding.

DR. ALAZRAKI: I understood from the presentations that we heard that those sensitivities and specificities that I think he just referred to, at least on the approximately 200 who had laparoscopy. That laparoscopy in that number was the gold standard.

Now there is another smaller group, I guess, who had hysterosalpingography as the gold standard. I suppose that in the labeling a reference could be made to both of those gold standards, indicating also the numbers on which they are based.

DR. CARSON: Dr. Schultz, did you have a comment?

DR. SCHULTZ: If I could, I think that the difficulty which you are obviously having with this sort of mirrors the difficulty that we were having with this as we looked at this issue. Again, I guess what we were looking for was some help from the clinical community in terms of as a potential user of this device, what method of displaying the data would you find the clearest and the most accurate?

I agree with Gary when he says I'm not sure this is really a statistical issue, as much as it is a clinical issue in terms of is the comparison to laparoscopy the

appropriate comparison? In the decisionmaking process, would you want to know how accurate this was in comparison to laparoscopy? Would you want to know how accurate it was in comparison to HSG?

I think that very clearly we can't put the 20 different tables in the label, and have anybody be expected either to read it or to understand it, since having had the opportunity to review this data for 3 months, we couldn't really come up with what we considered to be the best way to do it.

I guess what we are looking for here is some assistance from you all in terms of what do you see as the important or the most relevant method of describing the data, and how would you recommend putting that in the label? Clearly, we are not looking for a definitive answer here, but if you could give us some ideas, then I think we could go back and work with the company to develop an appropriate label.

DR. CARSON: Let me just suggest that I think that we have two standard tests that gynecologists are used to dealing with. One is an HSG, and one is a laparoscopy. We

have a new test that is going to be indicated for tubal patency. I think probably the most important information to give the user is what kind of range to expect compared against both of the standard tests.

What I would like to know is how often do I find a blocked tube on this test as compared to HSG, and then as compared to laparoscopy? How often I find a patent tube on this test as compared to HSG and laparoscopy? I could see that most easily done with a four cell chart.

DR. ALAZRAKI: I agree with that. Since this test would most likely in the work up replace the HSG, I think that that comparison is very important. I think the laparoscopy comparison is very important too.

I'm a little concerned in terms of what the real numbers are for the comparison data that we have with HSG, and whether from a statistical point of view there are enough to warrant credibility of those numbers.

MR. MONAHAN: I would ask everybody to speak clearly into the microphone, because the proceedings are being transcribed.

DR. J. LERNER: I just wanted to give you a little

bit of an overview for the non-clinicians on how I guess I see it as sort of the man out in the trenches actually doing it. I think that in very clear cut situations this will be a great first step. The way I refer to it is one stop shopping.

If a patient comes in and gets their basic infertility or most of a basic infertility work up -- the evaluation of the uterus with the saline, the evaluation of the physiology of the ovary, the proximity of the tube to the ovary, and then your tubal patency study.

If in fact you get bilateral spill or unilateral spill, or get what you suspect to be bilateral, proximal obstruction I think it gives you a pretty definitive answer, and you can kind of change your algorithm compared to what we would have done without this test.

I think that for all the other cases, where there is a question of what is going on, or your test is not conclusive, then we obviously just go back and use our, or what we consider, or what has proved to be as close to the gold standard, or that we have as much clinical experience in the past as that.

You are kind of getting caught up in ranges and this, and what are clinicians going to use. I think if it comes under physician usage in this way, which is I think it's most appropriate set up, I think the numbers aren't going to be all that critical, however you decide to do it.

DR. DESTOUET: I have a question for Dr. Lerner, please. Then do you think that the patients who have evidence of blockage, corneal obstruction, or proximal blockage would go directly to laparoscopy, or would they go to HSG?

DR. J. LERNER: Oh, I don't know. Again, I think in each situation, based on the patient history and what you expect, you can go either way. I don't know that there is a specific way to go on it.

I actually see it as the opposite way. You have a woman who comes in, who really has not particular anything in her background that makes you suspect one thing or the other, so you are kind of doing your baseline, and this is just one of the steps of your baseline first go round test.

So I can't tell you what I would do in any particular set if it was blockage here or blockage there or

whatever.

DR. DESTOUET: My question is directed because in the protocol it very specifically says that the use of laparoscopy in this country is quite low compared to the use of laparoscopy in Europe.

DR. J. LERNER: That's correct.

DR. DESTOUET: Now are we going to change those numbers? Are we suddenly going to go from low utilization of laparoscopy to increasing utilization of laparoscopy based on the Albunex?

DR. J. LERNER: No, I don't think we will, and I think probably certainly what will occur over the next X length of time is that we will use it as a screening test. If there is any question that it is not bilateral patency, or that the answers are not clear cut, then probably most physicians would go to HSG. That is just one person's opinion. I certainly can't speak for the 26,000 OB/GYNs in the United States, but that would be my take on it, but that isn't necessarily so.

I think once we get more experience and confidence with our own interpretation -- I think Dr. Parsons said

something at the beginning. If I could redo my number 1 patient as my number 25 patient, I have much more confidence in my ability to evaluate that test at number 25, than I did at number 1. So I think with time and with experience, as in anything we do in OB/GYN and medicine in general, we'll have more confidence in our results, and then be able to really taper the algorithm appropriately.

DR. CARSON: Thank you. Let me just remind the panel, and get back on track a little bit that we are really talking about asking -- FDA is asking us for our guidance as to how to really give the user the reliability or an idea of what this test is all about in terms of how to present this data.

Dr. Griem, I saw your hand up earlier. Did you have a question or a comment?

DR. GRIEM: Well, it seems to me one also has to look at the cost/benefit ratio. The hysterosalpingogram exposes the ovary to radiation and the genetic consequences of that. The laparoscopy has other risks involved, and additional economic expense.

I think you have to put that in the equation

somehow in looking at the various procedures. You may elect a procedure that is not quite as accurate, but doesn't have the radiation exposure, or doesn't have the additional cost, but has something that is quite useable.

DR. CHOYKE: I wanted to endorse your idea of a simple -- the percentage of tubes that were opened, that were confirmed, and percentage of tubes that were blocked, that were confirmed, and avoid terms like sensitivity and specificity, because they always confuse.

DR. CARSON: Okay, let's move on to question 4.

DR. KETTNER: Could we have our biostatistician demonstrate the --

DR. CARSON: I think we have concluded this question, and the panel has the guidance necessary.

Question 4, if approved for the new intended use, this device would in many instances, be used in an office setting, as opposed to a hospital or freestanding radiology suite. Does this raise any special safety concerns?

Any particular concerns that the panel has?

DR. CHOYKE: There were clearly big differences among some of the studies, which suggests to me that it is

difficult, and requires a lot of experience. For instance Dr. Parsons has a tubal concordance rate of 95 percent, where Dr. Thurman had only a 50 percent concordance. For patient concordance, Dr. Parsons had a 90 percent, and Dr. Thurman had a 25 percent. I want to go to Dr. Parsons.

The explanation that was afforded to us was that since the Albunex preceded the HSG in one study, and the HSG preceded the Albunex in the other, that explains that. That doesn't make sense to me, because it seems to me reducing this to the some simple case, this is a tube, and no matter what you put in it, should clear for the next study.

So the second study would disagree equally with the first study, no matter in which order they were done, unless there is some reason. Moreover, if you look on page 57, the negative predictive values range in the study from 14.3 percent to 100 percent depending on different sites, including Site H, which was a real problem. Again, presumably an experienced center, otherwise it wouldn't have been asked to participate.

So to me this bodes very poorly for how well this test will work out in the community. Will it require

special training of centers or other considerations? I think there is a lot of user variability.

DR. CARSON: I think those are very good comments for the next question. Right now we are just really on safety concerns. Any particular concerns that the panel has to address for safety that has not been addressed in the labeling?

DR. R. LERNER: As I radiologist, I am familiar with contrast reactions, and we have special equipment in our laboratories to handle these special trash carts and nurses were trained. I was just wondering if this should be an issue for contrast reaction with this Albunex? Obviously, some sensitivity studies have been done and haven't shown any, but there are idiosyncratic reactions, and these are rare. It takes many applications of these to detect these.

DR. HALBERG: I just wanted to read you the labeling. It says, "Hypersensitive reaction should be anticipated whenever a protein containing material such as Albunex are used in humans. Epinephrine, antihistamines and corticosteroids should be kept available for immediate

treatment of a patient's symptoms." That is in the labeling. I don't know if that addresses your concern.

DR. CARSON: So could I see a show of hands of those who agree that the special safety concerns have been taken care of by the present labeling?

[Whereupon there was a show of eight hands.]

Any who think there is something missing?

[Whereupon no one raised their hand.]

Okay, let's move on to Question 5. Use of this device, which combines the techniques of ultrasound and hysterosalpingography would be used by physicians with varying degrees of experience with each of these modalities. Do you believe that the instructions for use in the labeling are adequate? Or should the labeling include additional written instructions, or are other training methods needed?

I think it is very clear, as we have said, that this technique heavily relies on good ultrasonography, and that a lot of the data that we are looking at and have discussed in a previous question really is not device related as much as sonographic skill related.

If we look at the labeling, perhaps this is the

area where we most really need to consider, although it is difficult to know exactly what to suggest.

DR. PARSONS: These investigators represented everybody at the beginning of their learning curve. Nobody had ever done this procedure before they enrolled patients. So this is a worst possible result in a variety of centers, all of whom truly are interested in ultrasound, but it is a tricky procedure, just like the HSG that we rely on is. These are two screening tests with inherent difficulties.

DR. CARSON: Except that the centers probably had a little bit more ultrasonic skills than perhaps the general OB/GYN.

DR. PARSONS: They were a variety of radiologists, as well as gynecologists.

DR. CARSON: Also, Site H had 10 patients in which they did not want to state -- did not feel confident enough to even state patency or not, and that was a significant portion of their population.

MR. MONAHAN: Excuse me, could I interrupt for a moment, Dr. Carson. The people out in the other room are still having difficulty hearing. So I would request that

people speak directly into the microphone in a loud voice, louder than they have been using, and that they identify themselves when they begin speaking.

Thank you.

DR. DESTOUET: I have to point out that the radiologists who were included in the study are basically centers of excellence. These are radiologists who are either women's imagers or who are dedicated ultrasonographers. So we are not talking about a general practice radiologist in a small office. So I think clearly there has to be some kind of continuing medical education requirement built into the use of this procedure.

DR. CARSON: Just because the uterus has only one chamber, doesn't mean you need 25 percent of the skill of a cardiologist.

Any other questions or any other comments regarding this portion?

DR. KETTNER: I would like to comment on the training portion. Just like with Albunex when it was initially marketed for the cardiology indications, Mallinckrodt does have a large product support system, and

does intend to put out videotape similar to the one they put out with the Albunex when it was first released.

We have a 24 hour service, and we can hook people up with other doctors that might give them guidance. The procedure itself, a large part of the procedure is already a procedure that these physicians are familiar with. This is just an additional part of it.

DR. CARSON: Does the panel think we need to add something about specific mentioning about the skills of the ultrasonographer?

DR. ALAZRAKI: I think that there should be something in the labeling which indicates that the FDA strongly recommends that physicians who utilize this in conjunction with ultrasound have some training or seek some training and education in these procedures specifically.

DR. CARSON: A specific highlight that is pointing out that this device really does need to be used in concert with transvaginal ultrasonographic skill.

DR. HACKNEY: I'm not sure that's quite what I would want. We seem to have agreed that the people who were doing this in this study were very skilled at transvaginal

ultrasound. The question is becoming skilled at using this as an adjunct to it.

Perhaps the warning should say something along the lines that even for people with a great deal of experience with pelvic ultrasound, this still requires some extra training in order to become proficient at. Perhaps a specific indication that early results in the hands of experts were less than optimal. I don't think simply saying someone needs experience with ultrasound is enough.

DR. CULLINAN: I'm Jeanne Cullinan. I'm from Vanderbilt University. I am in both the Departments of Radiology and OB/GYN. I was part of the Mallinckrodt project for tubal patency and efficacy, and I am being supported today to testify here.

I think that the one thing that you need to recognize is that the question of whether or not radiologists or OB/GYNs who are performing this procedure indeed were skilled in ultrasound at the time of the procedure, when we first started. Even saline instillation utilizing ultrasound was relatively new at that time, and some of the centers had very little experience even using

saline instillation when we first started, let alone saline plus Albunex.

The learning curve that has been alluded to, all of us had to undergo that learning curve for the Albunex. Some centers actually had to undergo it even for saline instillation at the time of the first exams. Since that time, there has been a lot of interest and excitement in using saline instillation, and in many centers that is a routine procedure that is performed both by OB/GYNs, as well as radiologists.

I think that it is important to recognize that since that initial data was submitted, there has been even a learning curve in the general public utilizing some type of instillation and how you follow it, and what you are looking for.

DR. CARSON: Are you suggesting that besides a recommendation for expertise in ultrasound, the labeling also consider expertise in instillation?

DR. CULLINAN: Yes, and I think it's not dissimilar from the instillation techniques that have been utilized for hysterosalpingography. I think for people who

are versed in both ultrasound and hysterosalpingography, the transition is not as difficult as it might seem looking out on paper. Skills in both areas would be well suited to being able to perform this task.

DR. CARSON: Let me just read to the panel current labeling, and maybe we can have some suggestions.

"Diagnostic procedures that involve the use of Albunex should be carried out under the direction of a licensed practitioner having a thorough knowledge of the procedure and the safe use of the products."

Do you think that needs to be amplified at all?

DR. ALAZRAKI: I don't know. That is fairly good if we feel that it is necessary to emphasize, as Dr. Hackney just said, that even though you may be qualified with previous experience in doing these procedures and in ultrasonography, that for use of this particular contrast agent in this setting, we recommend in any case, some training and education in the specific use of this product.

I think it would be a good idea.

DR. HACKNEY: I agree with what I said before.

DR. CARSON: Is the panel ready to vote? Let me

ask you to limit your comments just to this issue, if you don't mind.

DR. J. LERNER: I guess the first thing I wanted to say was I ask you to look at what the hysterosalpingography devices are used, and have a labeling with that. I don't know offhand, but I'm sure you all do.

The second thing I wanted to say was just in defense of clinical practitioners. As any new technique evolves, certainly the vast majority of us do take training or courses or whatever it needs, so that we can learn the technique whether that is laparoscopy or anything else. So this is not dissimilar to any new technique.

DR. ALAZRAKI: In a sense it is, because even though the hysterosalpingographers probably are in the best position to do this, as long as they know ultrasound imaging, the office-based gynecologist may not be. I think probably it is reasonable to require some additional training in this.

DR. PARSONS: I would advise additional training for anybody undertaking it, no matter what their original training or the union they belong to. This is best done by

people that are specifically focused on reproductive imaging, whether it is a radiologist, a gynecologist, or even a sonographer. I don't think we can make generalizations about who is more prepared to do it.

DR. CARSON: One possibility -- let me just bring this up for the panel, is when the chart that we were considering is to specify that these rates were in the hands of people and used to transvaginal ultrasonography. That would be another option.

DR. CHOYKE: We are ignoring or assuming that all ultrasound equipment is the same. In fact, there is a wide variety of equipment that is out there. I suspect that the equipment used in the study was of the highest quality, but as it goes into the community, there is a tremendous range of adequacy. I think that raises a very important question about whether this should be done on all kinds of equipment of all images. That is a whole can of worms, I realize.

DR. CARSON: I don't really think that we have the week to address that issue, but it's a good point. I don't really think that we have the data either to do that, but I think again, is that something we want to include in the

labeling?

DR. CHOYKE: Well, there may be use issues of spatial resolution on a phantom that has to be approved for us. Of course that information isn't provided here, so that's an unknown that we just can't deal with right now.

DR. CARSON: Why don't we vote first on whether the labeling is adequate? Then if it's not adequate, we can suggest some changes to FDA.

Do you feel that the labeling as such takes into consideration the issues we discussed, and needs to be altered? Can we have a show of hands? It is under the direction of a licensed practitioner, having a thorough knowledge of the procedure and the safe use of the product. Is it adequate? Is the labeling adequate. A show of hands, yes? A show of hands no?

[Whereupon there were 0 yes, and 8 no votes.]

Can someone suggest what they would like to see in the labeling? We won't vote on this, but give some guidance to the FDA as to the changes.

DR. ALAZRAKI: I would suggest that there be a statement saying that it is strongly recommended that

physicians who utilize this material in conjunction with transvaginal ultrasound acquire some additional training and education in this procedure, with this product.

DR. HALBERG: I would support the addition of a request for additional training for practitioners.

DR. CARSON: Any other comments?

Let's move on to the next question. After reviewing the information provided by the sponsor, including the clinical and pre-clinical data, do you have any other recommendations for changing the labeling of this device? That is, all of the other issues of labeling, not this one. We have already talked about deleting the "possibly."

Also under precautions this talks about inserting an intrauterine catheter. Later in the labeling it talks about an intracervical catheter. It is my understanding that it is really an intracervical catheter, rather than an intrauterine catheter. Dr. Parsons, would you comment on that?

DR. PARSONS: This catheter is designed to be inserted into the uterus or the cervix. Often the balloon will slip up into the uterus, even if you don't want it to.

Many practitioners, having evaluated the uterine cavity with saline will then put the balloon in the uterus. I would prefer not to do that, but anatomy and experience dictates where it ends up really.

DR. CARSON: So you have technically no problem with keeping it consistent with an intrauterine catheter? I'm concerned that practitioners will use it like an HSG and just put it in without blocking the cervix. Maybe that doesn't matter.

DR. PARSONS: I think again, that even very experienced practitioners should be trained in the specific technique. I don't think the ability to do an HSG means that someone is going to be able to do this well. So I would leave details like this for the training of physicians.

DR. CARSON: So in the labeling, intrauterine catheters is okay with you in terms of technique-wise, your recommendation?

DR. PARSONS: Yes.

DR. CARSON: Any other comments on any other part of the labeling from the panel?

[Someone attempts to speak.]

DR. CARSON: Forgive me, I'm sorry. I thought you were with the company.

PARTICIPANT: If you don't want me to speak?

DR. CARSON: Yes, I would rather not.

PARTICIPANT: I have a suggestion for the label.

DR. CARSON: Thanks. Thank you for bringing that out.

PARTICIPANT: I've give the labeling to Dr. Ken Widder.

DR. HALBERG: Let me just add to the comments he added to the public record, if you submit them to the executive secretary, they will be included as part of the public record. So we welcome any additions to be submitted to Mr. Monahan.

DR. CHOYKE: Just one comment. I would like to see at the very least, a warning, notwithstanding that we are going to include the data, that there is a very high, and specify the false negative rate for determining whether blocked tubes exist.

I think practitioners should know right up front,

right under the indication and under warnings that there is a significant risk that a blocked tube will be incorrectly diagnosed with this technique.

DR. PARSONS: Can I speak to that?

DR. CARSON: Yes, Dr. Parsons.

DR. PARSONS: I would suggest that I think that is quite true. That is an inherent problem with this technique; also with HSG. It is no worse with this technique than it is with HSG. People are accustomed to that problem.

I would suggest you insert a statement from ASRM about guidelines for tubal screening procedures. This is a screening procedure, it is not a diagnostic procedure per se. So I would just say that a diagnosis of a tubal obstruction or uncertainty should be followed by some other test.

That is a recommendation to experts in the field when they are dealing with screening tests, and I think this is no different.

DR. CHOYKE: HSG had the good fortune to come about before all these gambles. It's unfortunate that

Mallinckrodt and MBI can't do it in the same way. Under these settings, I think it is appropriate to include that warning. If I was doing HSG now, I would probably recommend the same thing.

As far as your comment about whether it is a screening test versus a diagnostic test, I mean I think that all tests have false positives and false negatives; we accept that. This test has a very high false negative rate, depending on how you want to term it. I think practitioners have the right to know that that is the case.

DR. PARSONS: I agree.

DR. CHOYKE: So good. I think we should have a warning.

DR. CARSON: Let's ask the FDA about policy regarding ASRM guideline advice.

MR. MONAHAN: I really can't address that issue, but I would note that this is not a screen, because you are dealing with women who have presented with some symptoms. So you are not screening a normal population, and we make that distinction at the agency.

DR. CARSON: I think the ASRM guidelines are

certainly available. Whether or not that is appropriate to add, I think is probably an FDA issue.

The next question, has the evidence provided by the sponsor in the PMA adequately demonstrated the safety and effectiveness of the device when used for its intended purpose, which is diagnosis of tubal patency or blockage?

DR. ALAZRAKI: There is one troubling to me, and maybe I just don't really understand it as well, factor. That is that some of the studies apparently were done with saline flush and some were not. As I understand it, saline flush can actually undo a blockage, or open up and make a fallopian tube appear patent. Whether or not that fallopian tube stays patent or goes back to its resting state of being blocked is not at all clear to me. I don't know if it is clear to anyone here.

So I'm not sure whether or not the labeling should indicate something about saline flush. I'm not sure what the conventions are in terms of these procedures.

DR. CARSON: I believe the initial saline flush, the initial instillation of saline was used in all patients. That was followed by the device, but after the device some

used the second saline flush or not. So it is probably not an issue, since part of this technique is to start with the saline flush.

DR. PARSONS: You could probably use orange juice. It really doesn't matter. It's the same effect on the tubes.

DR. ALAZRAKI: As long as it is sterile, right?

DR. CARSON: Are we ready to vote?

DR. CHOYKE: I would just like to summarize my take on this. This is a test with a lot of false negatives. It is a test that has a tremendous variability among users. There are some still open questions about whether animal studies should be performed to verify that this has no impact on fertility, at least in animal studies.

I think that introducing this out into the public domain with a wide range of equipment is troubling. That is a summary basically of my concerns about the agent.

DR. HACKNEY: I share Dr. Choyke's concerns. My main concern about safety is to come back to what discussed earlier, that we don't have follow up beyond 24 hours except for one study in the women who were studied. It would seem

that we have a responsibility to at least know what happened to the people who have undergone this procedure.

If we conclude that there is no clear evidence that anything worse would happen than would have been expected from the hysterosalpingograms and laparoscopies, that is fine, that is something that can be reported.

I think if adverse effects did occur longer than 24 hours out in a study population, we simply didn't know about it, because we didn't bother to check. I would find it hard to justify that. I think one should at least expect the follow-up on the patients who have already been done.

DR. PARSONS: What adverse effects are you seeking specifically here that would happen in the long-term? Most of these patients are examined by the physician that takes care of them. There is follow-up practically speaking, after all of these procedures, but what are you looking for?

DR. HACKNEY: That is my point, is that I think this data exists that all of these patients were seen subsequently, and all I want to know is whether anything did happen. If the answer is no, that's fine. I would assume that would be the case, but I would rather know it than be

forced to assume it, because it isn't clear that if there were an unusually high rate of miscarriages for example in patients who had had this, I would at least like to know, or ectopic pregnancies. I would like to know that.

DR. PARSONS: How could you attribute it to this procedure though?

DR. HACKNEY: I may not be able to, but I would at least say that there was a study conducted, and I had the results of those patients. I would then look at each case and say, do I believe that the rate of ectopics that seems high was actually higher because of this study, or because of hysterosalpingograms?

If they never bothered to find out in a group of patients who are already identified and already studied, I find it hard to justify not checking. As you say, somebody knows. Every one of these patients was followed-up by their physicians who referred them into the study. Somebody knows what happened to these patients.

I'm not asking to go out and repeat the study with a long-term follow-up. I'm just asking what happens to the patients who have already done it. I gather they were only

followed for 24 hours. They have been followed for at least months now. What happened? If the answer is nothing out of the ordinary, nothing that you would not expect to see in patients who were treated the same way except for the Albunex, fine, but I find it hard to agree that we shouldn't care to know what the results were.

DR. PARSONS: Could I say something about ultrasound equipment?

DR. CARSON: Go ahead.

DR. PARSONS: And just about ultrasound procedures in general?

DR. CARSON: Sure, go ahead.

DR. PARSONS: Ultrasound is highly user-dependent, no matter whether you are using it as a means of using an adjunctive contrast or anything else. As you know, the results in just diagnosing any given problem with any given organ vary, especially reproductive ultrasound vary enormously from practitioner to practitioner.

So I think we are dealing with both problems of the ultrasound technique itself, as well as this. I think the issue is, can you see this in the tubes? The answer is

yes. Whether or not can you do ultrasound well plays into that and results in how much you can see, or how you draw your conclusions is something that any labeling cannot address.

I think that it has to be stressed that people need to be trained to do the procedure, but the substance itself cannot determine whether or not a person can use it.

DR. CHOYKE: No matter how good you are, if you machine doesn't have the resolution to see those tiny tubes that you showed, then you are not going to see one. You are not going to see them well.

DR. PARSONS: There is a variety of equipment that was used here. There was everything from small to large.

DR. CHOYKE: I think Dr. Saunder has -- all of your equipment is probably excellence.

DR. PARSONS: Some is, some isn't.

DR. CHOYKE: Speaking from personal experience, some of the equipment in GYN offices is not optimal -- not a criticism. For what it does, it's good. For big babies and determining biparietal diameters and things like that, it is perfectly adequate. To then go to an order of magnitude

requirement of resolution is a different story entirely.

DR. CARSON: I think that one thing I'm feeling from the committee is definitely the need for longer term follow-up. Let me just bring up the point that Dr. Lerner brought up earlier, is that many of these studies were done first by having an HSS, and then an immediate HSG. So following-up the patients that have already been tested is probably not going to answer the question of longer term follow-up.

So why don't we go ahead and vote on 7, assuming that the safety is within 24 hours. So has the evidence provided -- do you need to say something?

DR. HALBERG: Could I just ask the manufacturer if it is possible to obtain long-term follow-up on these women?

DR. KELLER(?): I'm Dr. Keller with Mallinckrodt. It is not possible with these specific women to rule out the effect of the various modalities. We can go back and look at these women though, to see if there were any follow-up problems, but I would caution you that we won't be able to really state what the modality was that caused the problem.

DR. CARSON: So let's answer Question 7 as has the

evidence provided in the PMA adequately demonstrated the safety within 24 hours, or we could say immediate safety, and effectiveness of the device when used for its intended purpose? Then we'll talk about perhaps longer term studies in Question 8.

DR. CHOYKE: What constitutes a longer term study?

DR. CARSON: I think we can talk about that in Question 8. Right now if we could just address the 24 hour issue, and then we can see whether or not we need more than that. I think the safety in terms of immediate safety.

DR. CHOYKE: But if someone has a concern about 24 hours being not long enough, then they have to vote no on 7.

DR. HALBERG: I think we're asking to address that in two specific phases, the first being 24 hours, and the second being if we need longer term follow-up.

DR. CHOYKE: So if you don't think 24 hours is adequate, you should say no?

DR. CARSON: No, I'm talking about the immediate safety, rather than the absolute, specific number. I'm talking about reactions such as infection, perforation.

DR. CHOYKE: Well, we're talking about other

things in addition.

DR. CARSON: Right, and I think those other things we can address in Number 8. So if we can just use Number 7 to the more immediate safety, and then the effectiveness of the device when used for its intended purpose.

Do you feel that evidence has been provided for the immediate safety and the effectiveness? All those voting yes, raise your hand. And no?

[Whereupon 7 hands were raised for yes; 1 hand for no.]

Now let's move on to Number 8. Are there any issues or concerns regarding the safety and/or effectiveness of this device that have not been completely resolved by the data in the PMA, and should be addressed through a long-term post-approval study?

DR. ALAZRAKI: I have one concern about the population that comprised the study population in that in the whole study population there are only 7 black women as I understand it, and very few Hispanic women. I just wonder since we are in an era of concern about populations, of course all the populations here are women; there is no

concern about men, but whether the same results would apply to a population of black women or Hispanic women?

Whether or not we should expand the study or get some information in future about this device and results in other populations not adequately represented?

DR. PARSONS: It was used in 30 African American women; at least the Albunex was infused. Others participated in other parts of the study.

DR. ALAZRAKI: I don't know if I can put my fingers on it right now, but the total comparisons to I think it was laparoscopy was only 7 black women, and I don't know about hysterosalpingography.

DR. PARSONS: Right. The 30 comprise every woman who received Albunex, whether or not they were compared with HSG or laparoscopy.

DR. ALAZRAKI: Were they all compared with something?

DR. PARSONS: Yes.

DR. ALAZRAKI: Still, it's a very small group relative to the population in this country. Now it may not be a large group relative to the population that seeks

infertility work up; I don't know that, but I still think that we might like to see the results in a larger group of those ethnic racial subgroups.

DR. DESTOUET: I also have a concern about the possibility of increased utilization of laparoscopy. I don't know if we can establish what the baseline levels of laparoscopy even in this country, but given the inherent difficulties in the study, the need that we have already addressed for training physicians to utilize this test. I think that the FDA needs to look at the utilization rate of laparoscopy following this procedure.

DR. KETTNER: I'd like to put up a demographic slide that would demonstrate more clearly. This demonstrates that in the United States phase 3 studies there were 22 of the 164 patients that were of African descent. In the United States phase 2 there as an addition 1. There were none in the European phase 3, 205 patients, but that was we felt, typical of a Sweden population. Then in the French study there were another 14 of African descent.

DR. ALAZRAKI: What I would like to do is find the chart that gave the comparisons, and actually what the base

of your calculations of sensitivity and specificity are. Go on, and when I find it, I'll bring it up.

DR. CARSON: Try page 18.

Any other issues? Dr. Choyke, you certainly have some issues.

DR. CHOYKE: Not really. I think they have all been addressed. The post-marketing phase of this, I think what is more important is what the peer reviewed literature is going to say. That is going to happen, whatever we say here.

DR. CARSON: Does the panel think there is a need for post-marketing surveillance in terms of one, the rate of laparoscopy as compared to HSG, and two, with regard to subsequent pregnancy outcomes? Those are the two issues that I have picked up in our discussions today. Any comments on that?

DR. PARSONS: My question is this. These studies weren't designed to evaluate causes of late term effects. So to really prove that would require a very well designed large study. Is there a scientific basis for suspecting that this product, or any basis for suspecting that this

product would have long-term effects in human tissue?

DR. CARSON: What we are calling for now is post-marketing surveillance. That is if the device has approval, to request from the company what kind of numbers after approval there is in terms of laparoscopy compared to the baseline for HSG, and what kind of pregnancy outcome after approval there is.

We're not saying set up a study. We're talking about survey what actually happens once the product is used in the population.

Any other issues?

So why don't we vote on whether these two issues should be addressed through long-term post-approval studies?

DR. HALBERG: We are now going to consider the panel's report and recommendations. The underlying data supporting a recommendation consists of information on data set forth on the application itself, summaries that were prepared by the FDA staff.

DR. CARSON: We are not quite ready for that.

DR. HALBERG: Oh, we're not?

DR. CARSON: No, we're still on Question 8.

Sorry.

Should the issues, that is should we call for a post-marketing surveillance for laparoscopy; a possible relative increase in laparoscopy after HSS versus HSG, and pregnancy follow-up after approval?

So does the panel think that we should address these issues through post-approval study? Those saying that we should, raise their hands.

DR. HACKNEY: We're asking about two different things for post-marketing approval. I would rather vote on them independently rather than together. You were asking both about laparoscopy rates and follow-up.

DR. CARSON: Let's first --

DR. ALAZRAKI: I just want to clarify exactly what will that do? I mean that would be interesting data, but why would we require that or ask that?

DR. DESTOUET: You mean regarding laparoscopy rates?

DR. ALAZRAKI: Yes.

DR. DESTOUET: I'm concerned that with the dissemination of this technique to the general public and

training of imagers, whether they be gynecologists and/or radiologists may not be optimal given the low level of specificity. That the algorithm may shift where more women who are having the Albunex HSG will go to laparoscopy, where before there was a very low rate of laparoscopy following HSG.

What that level will be, I don't know. Is it going to be acceptable? I don't know. It may well be, but if we have a five time increase in the rate of laparoscopy in this country, is that acceptable? We're talking about a fairly non-invasive test to an invasive test. I just don't want women to be guinea pigs. I don't them to have what looks like a relatively safe screening test, if we can say that, for fallopian tube patency, to now go to laparoscopy as a next step.

DR. PARSONS: I would just like to reiterate that what our data showed is that this is the equivalent of HSG as it is used now. It will not change practitioners' behaviors, because the specificity is identical to that that is seen in studies of HSG. It is no worse and no better.

So there is no substantive difference in the

effectiveness of this test in what we are now using. The fact is, we are using an approach that is biologically innocuous to get the data, that's all.

DR. DESTOUET: My understanding is that the specificity for HSG is higher than that for HSS.

DR. PARSONS: Not across the board in the literature. HSG has been used for 50 years. There was an attempt made at a meta analysis of its efficacy. It wasn't possible based on the hundreds of articles that had been published, but when three articles were compared in whom there were blinded assessments between HSG and laparoscopy, the confidence interval was something between 20 percent and 90 percent for specificity.

It is a very widely used test, but it is a very rough test. That's why I call it a screening test, because these women, the majority of them, don't have symptoms of tubal disease that undergo this test.

DR. DESTOUET: I have one other question. It says very clearly that the utilization of laparoscopy is low in this country.

DR. PARSONS: No, the utilization of laparoscopy

as a screening test for tubal patency is low. In other words, the first test to look at tubal patency is very low. In Europe with socialized medicine, the first test that is done in the U.K. and in Sweden is a laparoscopy in a patient presenting for infertility. In this country, we have a different approach.

Our study was actually designed -- we had hoped we've have more laparoscopies, but the fact is that it is not as often done in this country anymore, because we have better methods. I won't say it's better methods. We have a different approach. We can't afford to laparoscope every patient for infertility.

DR. DESTOUET: So you feel very strongly, Dr. Parsons, that we will not have an increase in laparoscopy?

DR. PARSONS: I feel that very strongly.

DR. DESTOUET: That really frightens me if we are going from low utilization of an invasive procedure to diagnose patency to higher utilization, particularly when the level of training out in the community of physicians who will be using this is going to be questionable, certainly in the beginning. I'm concerned.

I can only correlate this with some of the things we have done in breast imaging. I can tell you that you can go from centers of excellence, with terrific training to very variable training and very variable results as well. Now this may not be reflective for this procedure, but I would certainly like to see some data just to support that.

DR. PARSONS: That is the case for ultrasound in general. This is not special.

DR. DESTOUET: I rest my case then.

DR. ALAZRAKI: I think that the point that Dr. Destouet is making is certainly valid, but unfortunately I think it is probably, as Dr. Parsons said, very common that that happens. I'm not sure -- it would be very interesting to do that. I'm not sure that this group needs to require that.

DR. CARSON: Okay, well, let's just discuss the laparoscopy. Does the committee feel that post-marketing surveillance regarding the incidence of post-test laparoscopy be addressed through post-approval studies? Should we ask for that?

Please raise your hand if you think that these

studies regarding follow-up laparoscopy and the increase after HSS versus HSG be requested. And not be requested?

[Whereupon 3 raised their hands for yes, and 6 raised their hands for no.]

Now let's move on to the same question with pregnancy follow-up. Should post-marketing surveillance be done after HSS for pregnancy follow-up? Yes, please raise your hand? And no?

[Whereupon 3 raised their hand for yes, and 6 raised their hand for no.]

Now let me just summarize -- that ends our discussion, and I'll read Dr. Halberg to read this description -- what I think, and please correct me if this is not your understanding. I believe we have requested some labeling changes.

One was to delete the -- this isn't numbered, but on the label, page 2 in the gray box heads, "Precautions Gynecology," end of the second paragraph, the procedure possibly delayed until resolution of the infection be changed to delete the possibly, and rather that basically patients who have a gynecologic infection not have this

procedure until resolution of their infection. So delete the possibly is one change.

Two, to request training -- and I don't have the language, but FDA can address this -- address increased training in transvaginal ultrasonography, as well as the procedure itself HSS be included in the labeling.

Those are the two changes that I have. So if we can entertain a motion, and maybe Dr. Halberg can read now what the motion is, with these two changes in mind.

DR. HALBERG: Actually, I think I'll just read what we need to base our motion on, and then ask one of the panel members for a motion.

The underlying data supporting a recommendation consists of information and data set forth in the application itself, the written summaries prepared by the FDA staff, the presentations made today to the panel and the discussions held during the panel meeting, which will set forth during the transcript.

The recommendation of the panel can be approval, approval with conditions that are to be met by the applicant, such as those discussed by Dr. Carson, or denial

of approval.

How do you want to ask for a motion?

DR. CARSON: Let me move that with these two changes, that we approve the label. The motion is now open for discussion.

DR. HALBERG: Let me just restate the motion for the record. The motion is for approval with the following two conditions: deleting the word "possibly" as it relates to pelvic inflammatory disease and gynecologic infections; and also to require additional training.

DR. GRIEM: I'd like to second the motion.

DR. CARSON: Thank you. Now the motion is open for discussion. Any other issues?

Dr. Sternick, as our industry representative, any particular issues that you have?

DR. STERNICK: I think the issues have been fairly well addressed.

DR. CARSON: Could we have a vote? All in favor -
-

DR. HALBERG: Let me just mention that not all us have been voting as we have discussed the items you

presented, are actually qualified to vote. I'll only vote if there is a tie.

DR. SMATHERS: I thought we also agreed there would be some change in the information presented as far as the number of false positives. That is not part of the training, and it's not this one word.

DR. CARSON: That's right, thank you. Actually that was FDA. They asked us to give them advice. They had already decided that that should be included, and they asked us for guidance as to how to present it. So that is already in it. It's not really changed.

All in favor, raise your right hand. Opposed?

[Whereupon there were 7 yes, 0 no.]

Well, you are a great panel, and we have gotten through on time. Thank you.

DR. HALBERG: I would just like for the record to poll the panels, the reasons for their vote, and perhaps just make a brief of any length. We'll start with Dr. Destouet and move around the circle.

DR. DESTOUET: I think that we need a less invasive way to evaluate tubal patency, and that clearly

this looks like it may be efficacious, with my only concern being that there is a tremendous learning curve. I think with this procedure training is necessary. I hope that the peer review literature will show that there is no increase in the laparoscopy.

DR. HALBERG: Thank you. Dr. Smathers.

DR. SMATHERS: I think it is a minimal risk on an existing technique. It does appear to certainly make the ultrasound much easier to evaluate. I'm still troubled by the lack of specificity of the test. I would hope that with time that will improve, as the techniques improve.

DR. GRIEM: Well, I concur with the discussion, and I can't add anything else.

DR. R. LERNER: The risk/benefit ratio looks fine for what we have to deal with.

DR. ALAZRAKI: I think it is an improvement in the sense that as opposed to hysterosalpingography and radiation in women who want to become pregnant. So I think overall it is an improvement. Nothing is ever black and white, and I think there are a lot of gray zones still.

DR. HACKNEY: I agree that it's an improvement.

I'm not that concerned about the specificity, since one can always follow this up with a hysterosalpingogram, which would have been the first test if this weren't available.

DR. CARSON: I think it is an exciting alternative, with a very low risk/benefit ratio.

DR. HALBERG: Thank you. The recommendation of the panel is for approval with the aforementioned conditions. Thank you.

We will now break for the closed session of the meeting, which will not dealing with any of the items on the agenda here. We will come back at 1:00 p.m. and restart the afternoon session.

Thank you.

[Whereupon the meeting was recessed for lunch at 12:00 p.m., to reconvene at 1:00 p.m. in closed session.]

A F T E R N O O N S E S S I O N [1:10 p.m.]

Agenda Item: Molecular Biosystems, Inc.,
Presentation for P960045

DR. HALBERG: This afternoon we will be considering the original PMA submitted by Molecular Biosystems for use of FS069 in echocardiography. The presenters for MBI, the sponsor of the supplement I believe are already at the presenter's table. Once again, when you all have finished your presentations, if you could give the table over to the FDA presenters, that would be appreciated.

We will start with Dr. William Kirkpatrick who will begin the company's presentation and the information contained in the PMA that we will be considering this afternoon. Dr. Kirkpatrick.

Agenda Item: Introduction/Agenda

DR. KIRKPATRICK: Good afternoon. I am Bill Kirkpatrick, Director of Regulatory Affairs for Molecular Biosystems Incorporated located in San Diego, California. First of all, I want to thank the FDA and the Center for Devices and Radiological Health for arranging for this administrative review of our PMA for FS069. In addition, I

would like to thank the ladies and gentlemen of the panel for their contribution and participation in the process.

Shown on the board are the participants from Molecular Biosystems present here today. In addition, we have other staff members in the audience who are not listed on this slide.

Shown here are the consultants who are with us today. These individuals are available for resolving questions or issues during the discussion period. We would ask that the panel hold its questions until after we finish our presentation.

This is the agenda that we will be following during the next 30 minutes. I will provide a brief product description and then our Vice President for Research, Medical and Regulatory Affairs, Dr. Harry Dittrich, will review the preclinical data, the clinical data, and the conclusions which arise from our studies.

First of all, I would like to say a brief word about ALBUNEX, which is a first-generation product. It was first approved for ultrasound -- cardio indications for ultrasound imaging. ALBUNEX is an air-filled suspension of

air-filled albumin microspheres which are well-defined, well-characterized and echogenic immediately following their manufacture.

The indication for which ALBUNEX is approved is for cardiac imaging. Its marketing authorization in the U.S. was obtained in August of 1994.

ALBUNEX has also been approved for marketing in the United Kingdom, in Sweden, Finland, Japan, Mexico, and most recently in Canada.

Today, 27,000 units have been distributed in the United States. This equates to an estimated 17,000 patient administrations which have been completed without significant problematic adverse events.

For comparison purposes, we show here the first-generation ultrasound imaging product, ALBUNEX, and the second-generation product, FS069 which is under review here today. Both products are composed of well-defined, well-characterized microspheres and neither product is an emulsion.

ALBUNEX has air-containing microspheres, whereas for FS069 PFP is contained within the microspheres.

ALBUNEX is suspended in five percent human albumin, whereas the microspheres of FS069 are suspended in one percent human albumin.

As you can see, the concentrations for the two products are very similar in terms of microspheres per mL and the main particle sizes for the two agents are also very similar. This is the size of the well-defined microspheres.

The duration of effects for the two agents are shown here, ALBUNEX having a duration of effect of 40 to 45 seconds, whereas, the imaging efficacy of FS069 endures for more than four minutes.

Shown here are the dose schedules for the two agents. For ALBUNEX, it is based on the 70 kilogram patient and the dosing schedule is five mLs approximately initially, followed by an incremental dose of 15 mLs, up to a total procedural dose of 21 milliliters.

The dosing schedule for FL069 is not based on patient weight. In fact, the initial dose is one-half of a mL, followed by a 3 mL increments, up to a procedure maximum of nine milliliters.

I wanted to point out the encapsulated gas volume

in the two agents. For ALBUNEX, again, based on the incremental dose of 15 mLs, the microspheres encapsulate 500 microliters or one half of a mL of air. For FS069, based again on the incremental dose of 3 mLs, encapsulated is 100 microliters, or a 10th of a milliliter of perfluoropropane. Perfluoropropane is an inert, relatively insoluble gas.

Shown here are the indications that we are seeking for review here today.

At this point, I would like to turn the podium over to Dr. Howard Dittrich, who is our Vice President for Medical Research and Regulatory Affairs.

A brief word about Dr. Dittrich's background. From 1984 until 1996, Dr. Dittrich held a staff position in the Division of Cardiology at the University of California, San Diego School of Medicine. During that time, from 1990 until 1996, he served as a consultant to Molecular Biosystems. In 1996, he joined Molecular Biosystems as a full-time member of our staff. Dr. Dittrich continues to maintain an appointment as a clinical professor of medicine at the University of California, San Diego, where he sees patient on a weekly basis. Dr. Dittrich.

Agenda Item: Preclinical Toxicology/Clinical
Studies

DR. DITTRICH: Thank you, Dr. Kirkpatrick.

As you see, these are the indications for which we are seeking approval today. Let me cover those. FS069 is indicated to be used in conjunction with echocardiography to provide opacification of cardiac chambers, improved delineation of endocardial borders with concomitant improvement in visualization of wall motion to enhance the doppler signal and to convert nondiagnostic to diagnostic images.

I think it is appropriate at this time to discuss a little bit about the clinical problem we face with ultrasound contrast. I guess it is also relevant to move you back from the one-chamber organ to the four-chamber organ of the heart.

On the left you see an ultrasound image from a patient with excellent endocardial definition. You can see from this still frame a nicely defined endocardium of the left ventricle. This is seen in some patients but not the majority, actually, quite a minority. In fact, more

patients have suboptimal endocardial delineation. The patient on the right has minimal endocardial delineation. There is a septum here, but we are not sure we are seeing the endocardium, and we are certainly not seeing it anywhere here. The most that can be said about this is that the left ventricle may be large, but little can be said about regional and global left ventricle function. That is important from a clinical standpoint.

It is important to see all of the endocardium because there are important diagnostic and even therapeutic decisions made based on the ability to see all segments and the ability to make a decision concerning for instance the presence of single or multi-vessel disease. So this is a real problem in clinical cardiology and there is, therefore, a need to enhance the endocardium especially in patients with poor endocardial delineation.

I will give you an example. We will begin with a little video of actually the patient I showed on the right of the slide. This is a patient actually from our phase three study. We will not show any contrast here. But you will get an idea about the limitations in patients like

this.

We can see, for instance, in real-time imaging, that the left ventricle appears enlarged, but little can be said about regional systolic function. Certainly, one could surmise from this there is limited global systolic function, but not much more can be said, and that may be true in multiple views.

This, on the other hand, is now a patient from the phase three -- one of the two phase three clinical trials. We look at endocardium before contrast that can be well visualized. This is a patient on day one before ALBUNEX. This is the patient 48 hours later after FS069.

You will see ALBUNEX injected here about 15 mLs, and 0.5 mLs of FS069 here. With ALBUNEX you see some opacification of the left ventricle, but it is limited basically to this segment and not very intense. What you end up seeing is some enhancement of this lateral endocardium. That is to be compared with FS069 on the right. You can see by now that the ALBUNEX effect is gone while, with FS069, again, after 0.5 mL total dose, we now see a complete endocardial delineation. You can see

thickening of the septum. We are in a four-chamber view.

We will go now to a two-chamber view where I see anterolateral papillary muscle, posteromedial papillary muscle, and can draw conclusions about wall motion, myocardial thickening through complete opacification and clear endocardial delineation.

Finally, we can rotate to a parasternal short axis view where there is continued complete opacification and then finally a subcostal four-chamber view.

I would like to turn now at the outset to the extensive pre-clinical studies which were performed to support the filing for FS069 and point out that, in summary, FS069 is nonteratogenic, nongenotoxic and nonirritant. There is an extremely wide safety margin in both acute and repeated studies of 100 to 400 times greater than the human dosage for left ventricular opacification.

Our preclinical studies demonstrated that the components of FS069 are rapidly eliminated by the lungs. That is the perfluoropropane within the microsphere, and by urinary excretion following metabolism by the liver. That is the albumin component.

This is an example from anesthetized dog study in which we did extensive pharmacokinetics to demonstrate the half-life. Here you see half time with near complete recovery of perfluoropropane in 20 to 36 seconds after these high doses. Notice how little perfluoropropane can be detected within the venous blood after an injection at various volumes.

This is an overview of the extensive preclinical studies which were performed on FS069. We found in a genetic toxicology study that FS069 was nongenotoxic. In an acute I.V. study we found no adverse effects in rats, dogs, monkeys, at dosages up to 20 mL per kilogram. Again, that is 400 times the 3 mL per 60 kilogram individual. We are seeking an indication for left ventricular function.

A repeated I.V. study showed no adverse effects in rats at five mL per kilogram and dogs 20 mL per kilogram.

The teratology study showed no effects on the developing embryo in rats at 10 mL per kilogram and rabbits at 5 mL per kilogram.

There was an incidence of spontaneous abortions at the very high dose in rabbits, as well as death at the very

high dose in the maternal rat study.

Hemodynamic studies were performed that showed no alterations in hemodynamic parameters, blood gasses at 0.25 mL per kilogram and the irritation studies giving FS069 I.V. IM into the skin. And intraocular showed no irritant -- that FS069 was a non-irritant in rabbits, compatible with human blood.

Let me turn now from that review of the extensive preclinical studies to our clinical development plan. The remainder of the talk will be focused on that.

We did a total of 308 patients in these six studies. The first was a phase one safety and dose ranging comprised of 40 normals, of whom 16 underwent immunologic testing, which I will detail later.

One-year after the phase one study, we performed a study in five of these first 16 in which we did a rechallenge in order to test for immunology in response to FS069 after rechallenge.

We also did a phase one study in 10 normals looking at the mass balance of FS069, particularly perfluoropropane. We then performed phase one/phase two

immunology and safety study in which we compared FS069 to the control one percent human albumin in 50 subjects, some of whom were patients and some normals.

Finally, we performed two identical, well-controlled phase three studies with 101 and 102 patients in which we compared FS069 versus ALBUNEX for the indications of endocardial border delineation, left ventricular opacification and doppler.

This is a summary of the extensive safety evaluations by protocol. You can see we did 12-lead electrocardiography, physical exam in all studies, extensive, detailed neurological exam in normals in the phase one safety study, spirometry in the phase one and phase one-two study, vital signs. Importantly, oxygen saturation throughout and after each injection in all of the studies, and for the purpose of this, even -- I am talking about six studies -- I have now pooled these two identical, well-controlled phase three studies for the remainder of this talk to give you both safety and efficacy results together.

So, again, oxygen saturation throughout all of

these studies, and then extensive chemistry panel, hematology, CK with isoenzymes, urinalysis and coagulation. All of these were performed at baseline at 30 minutes and then particularly in the phase three study at least 48 hours after the last agent was received.

We had outside reviewers, Dr. Saravis, who is in the audience, for immunologic testing; recovery and half-life of perfluoropropane, Dr. Grevel. SmithKline Beecham was our central laboratory. Our core laboratory for the phase three study was at Georgetown University, and Dr. Jan Callahan has done the statistics.

In addition, we obtained the services of an independent safety review that reviewed all six cardiac function PMA studies and specifically reviewed detailed case report forms from samplings of all of the studies, especially the phase three study. This was performed by Duke University Medical Center and chaired by Dr. Califf.

The conclusions from that independent safety review was that FS069 is safe and comparable and mild side effects to ALBUNEX and is acceptable for use in the general medical community.

Let me turn now to the phase one FS1000 study. This, again, was a safety dose ranging and immunology study in which in the immunology component we looked at the immunoglobulin shown here. This involved 40 normal healthy subjects, 25 females, 15 males; immunologic testing done in eight males and eight females.

We used a staircase logarithmic dosing schedule with group A receiving .5 and 5 mLs; B, one and 10; C, two and 20; D, four and 40. I think that it is important to reiterate that doses we are planning to use for cardiac function ranged between 0.5 to 3 mLs or a cumulative of nine mLs. But our initial studies included cumulative volumes to 44 mLs.

These were the adverse device events from the phase one study. You can see the rate varied from none here to the highest of 17.5 percent at the 40 mL dose. Importantly, the ADEs were classified as mild or moderate and comprised of headache, nausea, light-headedness, warm sensation, similar to those reported for ALBUNEX in the past. As well, in the group of 16, there was no evidence of antibody production to FS069.

In the FS1250, the rechallenge of patients.

Remember, we took five normal, healthy subjects from the phase one study, rechallenged them a year later with 20 mLs of intravenous FS069. Extensive immunologic testing found no evidence for antibody production, cytokine production or complement activation.

The FS1500 was the mass balance study intended to determine perfluoropropane in blood and exhaled air as well as the half-life and recovery of perfluoropropane. We looked at 10 normal, healthy subjects, again, giving a high dose, 20 mLs intravenously and measured exhaled air and intravenous blood that was collected from 180 seconds before injection out to 600 seconds following FS069.

The results of that study. We were able to recover 93.4 percent of PFP and actually, excluding subject three, who had a leaky collection bag, the recovery rate was 98.5 percent. The half-life of PFP was 1.3 minutes. And PFP was detected in blood at very low levels at early time points and was no longer detected by 10 minutes, with our lower limit of detectability at three parts per million.

The FS6000, a phase one/two immunology safety

study, was to look at immunology and safety compared to the control. Remember, FS069 is carried in one percent human albumin.

The population was 50 participants, including 20 normal subjects, 10 cardiac, which are patients with cardiac dysfunction, typically ejection fraction in the 30 to 40 percent range; 10 respiratory patients with various forms of chronic lung disease, be it obstructive, bronchitic, asthmatic, pulmonary hypertensive, and 10 patients with varying degrees of hepatic dysfunction.

Dosing was, again, 20 mLs of either intravenous FS069 or one percent albumin. This was done in a randomized manner.

You can see the immunoglobulin testing that was done and taking from six plasma samples drawn 24 hours before the study out to three weeks post-study. In addition, we looked at cytokine and complement activation analyses as shown here.

The results from that study showed that there was no statistically-significant difference between the ADEs with FS069 versus human albumin control and that all ADEs

were mild or moderate, described as headache, cold feeling, lightheaded being the most frequent. Importantly, immunologic studies showed no evidence found of antibody production to FS069, increased cytokine production or complement activation.

Finally, turning to the two controlled phase three studies. We looked at the safety and efficacy for endocardial border delineation, left ventricular opacification and doppler signal enhancement. This was a crossover study -- two crossover studies. They were two identical, comparative multi-center trials involving males or females greater than 18 years of age who were referred to an echo lab for a diagnostic echocardiogram.

We required that a minimum of 33 percent or two of six left ventricular endocardial segments be not well-visualized at baseline in order for patients to be enrolled. In addition, we specifically mandated that a minimum of 25 percent of the population enrolled by those with either chronic pulmonary disease and/or cardiomyopathy. These patients had pulmonary hypertension, chronic obstructive lung disease, asthma, bronchiectasis or other debilitating

pulmonary disease. Those with cardiomyopathy had to have a left ventricular ejection fraction between 20 and 40 percent and could be composed of either ischemic or idiopathic cardiomyopathy.

The intravenous dosing given for FS069 was .2 to five mLs for a cumulative of 8.7 mLs. Then, at least 48 hours later or before, depending on randomization, ALBUNEX in the approved doses, which is given per kilogram, was given at a cumulative volume of .3 mL per kilo or for a 70 kilogram person about 20 mLs.

We use consecutive enrollment from the echo lab, and each patient received both FS069 and ALBUNEX a minimum of 48 hours apart in a randomized fashion.

We looked at the safety assessments I have shown you previously. Those, again, were done at baseline 30 minutes and 48 hours. In addition, oxygen saturation was evaluated on a minute-by-minute basis after each injection.

The investigator was required to review the test agent one safety assessments prior to administration of test agent two and all of the efficacy assessments we made and showed today were made by an independent core laboratory.

These are the sites from the two trials. You can see that it is comprised of both academic centers, private institutions, as well as VAs.

These were the demographics for the population studied -- 78 percent males. You can see that we required 25 percent to be from the impaired function subgroup, that is either cardiac and/or pulmonary disease, but we in fact enrolled 36 percent who fit into that group. The ethnicity of the population is shown here.

Now, to give you the safety results. Again, I put this up here to show you the timing sequence. We did baseline evaluation. The test agent, for instance, O2 saturation may have been performed along here, but bloods were drawn at 30 minutes. At least 48 hours passed before they had a reevaluation, and the new agent or second agent 30 minutes, and then a minimum of 48-hour follow-up after the second.

For the clinical parameters, a physical exam, 12-lead electrocardiogram, vital signs, and oxygen saturation. There were no statistically-significant differences after FS069 from baseline.

These are the safety result -- the laboratory parameters. On the left side you see those which had no statistically-significant changes, total CK, all isoenzymes, the urinalysis, all of these chemistry panel parameters, the CBC parameters, and the coagulation parameters.

These were results that were statistically-significant but clinically irrelevant. By way of example, the PTT was found to change significantly by 0.25 seconds, which is, of course, clinically irrelevant.

The calcium, for instance, increased by 0.13 milligrams per deciliter after 30 minutes, and decreased by 0.13 milligrams per deciliter after 48 hours. So, although they were statistically significant, they were clinically not relevant.

This is a slide of the adverse device events. In the upper left you see the ALBUNEX patients. Ninety-one percent had no ADEs. There were nine percent with ADEs of which five percent were agent related.

For FS069, 93.5 percent had no ADEs, 6.5 percent with ADEs, of which 4.5 percent were agent-related as determined by the investigator at the time of the study.

Looking at the impaired-function subgroup on the lower two cookies, there were 90.5 percent with no ADEs, 9.5 percent with ADEs, of which 5.4 percent were related after ALBUNEX. After FS069, 97.3 percent of these patients with cardiac and/or pulmonary disease had no ADEs. 2.7 percent had ADEs of which 1.4 were agent-related.

I think it is important to give you an example of the kind of ADEs we saw. This was for the FS3000 study, one of the two identical studies performed. The most common were transient, altered taste, warm sensation, flushing and headache. You can see we listed all of them. We have a left elbow cut, so we showed all of them here, not just those related to the agent itself, and for ALBUNEX as well as a comparator.

For the FS3,500, the device events are shown here.

Now, the efficacy results. Again, these claims in the PMA are based upon a core lab review which is amassed to test the agent identity, dose, and patient history.

This is an example I would like to show to demonstrate how we evaluated the primary end point which was endocardial length. On the left is a non-contrast image.

We asked the core laboratory to measure in centimeters the length of endocardium that could be well-seen in their judgment. And then, again, at a separate time, blinded to this result, they were asked to review either ALBUNEX or FS069 at all of the doses and draw the length of the well-visualized endocardium.

The difference between these two lengths was used as the change from baseline and the primary efficacy endpoint.

You can see here on the left in the blue the change from baseline in centimeters for ALBUNEX at the two doses, ranging between 2.2 and 3.4 centimeters. And the change from baseline for FS069 ranged from six centimeters at .2 mLs to 7.5 and 7.6 at three and five mLs respectively. These were highly statistically-significant, but differed between FS069 and ALBUNEX.

In addition to measurement of endocardial length, we divided the left ventricle into standard six segments and asked the core laboratory to define whether these were inadequately seen, adequately seen, well seen on a four-point scale among the six segments from this apical four-

chamber view. When we did that we looked at the percent of patients with one or more of those six segments improving. Again, these are pooled for the two phase three studies.

With ALBUNEX, all patients in burgundy, you see 52 and 64 percent had one or more segments improving. The impaired function subgroup, those in whom ALBUNEX is thought to be less-effective, had 47 and 64 percent. For FS069, all patients ranged between 80 to 96 percent and, importantly, in the impaired function subgroup, there were essentially the same results between 75 and 97 percent. Again, the difference between endocardial delineation and improvement was highly statistically significantly different between FS069 and ALBUNEX.

A secondary end point we measured was left ventricular opacification. This is an image pre-contrast. This is a patient who received ALBUNEX. You see opacification about two-thirds of the way into the left ventricle, but there is some missing along the lateral edge. After FS069, you see a hundred percent filling. We asked for gradings of one-third, two-thirds, or complete filling as a secondary endpoint.

This shows a slide of greater than -- equal two or greater than two-thirds filling of the left ventricle. Here you can see where patients with impaired function tend to do worse with ALBUNEX. Instead of 41 to 56 in all patients it dropped in the impaired function subgroup here, while with FS069 there was consistent and highly significantly-improved left ventricular opacification for all patients as well as those with the impaired function subgroup.

The doppler signal enhancement from these two studies. I am showing you only the three mL for the sake of limiting the numbers, the three mL dose of FS069. We asked the study, the core lab to tell us of those patients with inadequate signals, non-contrast, how well did FS069 convert those patients to adequate signals.

Let me go through these. It turns out that for the mitral valve, only one percent of patients had inadequate signals. In both cases or in a hundred percent of those, FS069 converted them to adequate. Eight of the approximately 180 people who had the doppler study had inadequate signals at baseline. A hundred percent of those converted.

For the right pulmonary vein, there were 50 patients or 28 percent with inadequate baseline signals, of whom 68 percent converted.

For the left pulmonary vein, 47 percent were inadequate, of whom 81 percent converted to adequate after three mLs of FS069.

Here is just an example of a doppler pre-contrast with essentially no wave form. We looked for a typical M-shaped in-flow with one component in systole and one in diastole. After FS069, we now see these. We actually not only see those, but here is the whole systolic jet of mitral regurgitation regurgitating into the pulmonary vein. So there is important potential diagnostic information in the signal not appreciated before FS069.

Then we also asked the core lab and the statisticians to help us define a population who we would call truly nondiagnostic at baseline. These are people who have only two or less of the total endocardial segments of the six segments adequately visualized. So they may have zero, one or two out of the six adequately seen. We asked how many of those would convert to at least five of six

endocardial segments adequately visualized -- so the extreme of endocardial segment improvement. We had 85 such subjects, of whom FS069 converted 63 or 74 percent from what was predetermined as a non-diagnostic study to a diagnostic study.

I would like to turn the video on now and show the next clip which was actually a patient who has both impaired function and who meets the criteria for a non-diagnostic image. What we can say about this image is that we do see a papillary muscle, but we do not see much in the way of endocardium. We can say it is enlarged and globally there is some depression. But, after .5 mLs of FS069 we now see in detail endocardial delineation in the septum, around the apex, after complete opacification outline of the papillary muscle and we will be able to go as well into a two-chamber view shown here where there is complete delineation, now with the contrast effect outline the endocardium.

These are important points from a prognostic view.

This is another example. In this case, we often have trouble with artifact in the apex of the left

ventricle. Certainly there is a difference in therapy. We now recommend echocardiography after anterior MI to rule out apical thrombus. I point out over these -- in the apex, a question of artifact versus thrombus. Through the complete left ventricular opacification and complete endocardial delineation, one will now be able to see that, in fact, this is an artifact. As we see the FS069 enter the left ventricle, we see the contrast sweep through what is clearly an artifact to show now, in fact, a very thin and dyskinetic apical segment which is representative of this patient's apical infarct.

Simply the matter of seeing the FS069 flush through what may have been misconstrued as a thrombus proves that it was in fact artifact.

I would like to conclude by saying that we believe very strongly that the PMA submission concludes and concludes strongly that FS069 is safe. We have extensive preclinical studies and we demonstrate 100 to 400 times the recommended clinical dose given safely. We have clinical doses 14 times the recommended dose. We have a low rate of ADEs, similar in nature to ALBUNEX, and have support by an

independent safety review committee.

The efficacy demonstrates that FS069 has superior efficacy to ALBUNEX at doses shown. We believe that this information provides strength for the indication which is, again, to provide opacification of cardiac chambers, improved delineation of endocardial borders with concomitant improvement in visualization of wall motion, enhancement of the doppler signal and conversion of a nondiagnostic to a diagnostic study.

Thank you. We will conclude at that point.

DR. HALBERG: Thank you. Dr. William Sacks, the FDA's lead reviewer for PMA 960045 will provide an overview from the FDA's perspective.

Agenda Item: FDA Presentation - PMA Overview

DR. SACKS: Good afternoon. Just to give you an overview without being too repetitious here, of Dr. Dittrich's presentation, the FS069 is an ultrasound contrast agent. It is made of microbubbles that have an albumin shell and are filled with perfluoropropane, an inert, and relatively insoluble gas.

Perfluoropropane, for those who do not know, have

been approved by the FDA for intraocular use.

I would like to make one comment about the physics of microbubbles as a contrast agent. Most of the structures that offer echoes in ultrasound are interfaces where the speed of sound changes. That is called specular reflection. Microbubbles, in fact, work on a completely different principle, and that is that they, first of all, are too small to give any kind of specular reflection. They act as little antennas that actually absorb sound energy by expanding rapidly and compressing rapidly. If they are the right size, they do this in the exact same frequency as the incident sound beam and they, therefore, radiate, they absorb and re-radiate in both the forward and backward direction significant amounts of this energy. That is the mechanism through which microbubbles, whether we are talking about ALBUNEX or FS069 happen to give their result. That was also true in this morning's talk I might point out.

This overhead gives a list of the reviewers from the FDA who looked over this submission. As you can see, in the right-hand column, we dealt with both physics, the clinical issues, toxicology, heavy dose of pharmacokinetics,

as you can see, statistical issues, pharmacology and toxicology, chemistry, and microbiology, and we had reviewers both from CERH, who are the ODE, OST and OSB reviewers, as well as reviewers from the drug section of the FDA.

We are going to have two speakers this afternoon from the FDA. Dr. Dan Spyker is going to talk about the pharmacokinetics, and Dr. Steve Kurtzman is going to talk about the clinical studies. Let me just first put on the slide again. This is the same slide that you saw before. Just to highlight one issue, the first four of these were phase-one, phase two trials. It is the bottom two who were the phase three trials that included not just safety issues, but efficacy.

Agenda Item: Preclinical Studies

DR. SPYKER: This is a subset of the reviewers that Bill mentioned who are responsible for the toxicology, pharmacokinetics and clinical summary section. Our intent is to, of course, be complementary with a very thorough presentation that you heard from the sponsor. I am going to try to try to give you the perspective of what we do as a

review team to get from the data, from the case report forms, to the label. That is really where our focus is.

I have been punished for having my handout ready early. It did not get out to you until a few moments ago.

I am going to cover these first few points here and the last couple of points, endocardiographic study will be covered by my colleague, Dr. Kurtzman, cardiographic colleague I might say.

I cannot forego my clinical pharmacology roots and not show you the picture of the molecule. We are talking about perfluoropropane, three carbons surrounded by as many fluorides as it takes. This is chemically stable, including its use as a high-voltage insulation. It is broken down by photolysis, so it is not necessarily a concern to us in the environment.

Most important to us is that it seems to be impervious to oxidases, the P-450 kinds of stuff. Those are, as you know, effectively oxidizing carbon-hydrogen bonds. I see that my assistant has not quite gotten these corrected.

[Laughter.]

DR. SPYKER: We did, of course, look at the material provided by the sponsor, but we also had our own experts do a thorough literature search through dozens of databases and 200-plus citations. We did not find anything that surprised us or caused great concern.

The product, in a 3-mL dose is approved, called I-Span, in the treatment of detached retinas. In February of 1993 that product was approved.

Medication device reporting for this period shows only four reports, gas diminished too fast, with a complaint in three of them and hardened -- the gas hardening as a report in one case.

We also consulted some of our experts in metabolism and anesthesia. In my previous life I was working with the anesthesia group and drugs, and fluoride toxicity was of concern to us in many anesthetic agents. I am pretty comfortable, based on consulting these kinds of experts, that we do not have a problem.

So the bottom line is, as far as we can tell, PFP is stable in the body and unlikely to present a toxic hazard.

The way we thought of the clinical studies is summarized here. By the way, this is not meant to be legible. We passed out these handouts for the panel. The rest of you will have to believe me I guess. But we think of sort of four clinical trials. This is the follow-up, as you heard mentioned, from the FS1000 study. I put this up here to tell you what I am going to focus on in terms of pharmacokinetics this particular study, the 10 normal volunteer study called by the sponsor as FS1500. Safety and immunology you have heard about. Principally, we are going to focus on the last study because that is the most of the information we used in labeling this product.

As you have heard, the sponsor studied PFP kinetics in animals and humans. Recovery in inspired air -- if we look at the nine patients where we had a pretty good, pretty complete data collection, the average PFP recovered within a 10-minute period after a 20-mL injection, and recall we are labeling them for a half to three mLs as a single injection, was about 98 percent on average or the median value, and 70 percent of the 136 range over those nine patients studied.

The concentration of respired air. As you have seen, we believe -- we are pretty comfortable with the PFP in inspired air is a pretty good measure of the PFP levels in the blood, and it is much more accurately measurable. For a given blood level, we can get a higher or a more sensitive assay in the air. So, insofar as we believe the half-life of the air or expired PFP is a good marker or surrogate for half-life of the blood. We believe that PFP disappears at a half-life of about one minute. That, again, is from the nine patients with pretty complete data collection in the FS1500.

Now, why do we even worry about the pharmacokinetics or the time course of the levels of this. Again, this is a graphic of the expired air concentrations of PFP in a particular patient in study FS1500. So, as you may recall, the infusion rate was a 1 mL per second rate in these. So the infusion duration for this study was 20 seconds. A third of a minute was the duration of effusion actually out to this point here. We measured the PFP in expired air at 10, 20, and 30, as you can see, 40, 60, 90 seconds.

So these are the measured PFP in this particular patient. I have shown error bars here just sort of as a reminder to me to tell you that, in general, our accuracy gets a little wider as we get down. I am reminding you that this is a logarithmic plot, one, 10, 100. And when you see the disappearance of PFP, it does not follow a straight line. If this were a well-behaved or one-compartment product, then this would be a straight line all the way down. We saw pretty consistently across the patients studied that this, in fact, seemed to have a tail at the end or means to us a second compartment.

So the reason we are concerned about this, the reason we care about pharmacokinetics, aside from making jobs for people like me, is simply to have some real comfort. Since we know that 98 percent of this PFP is gone in 10 minutes, and we see the half-life responding fairly promptly and consistently across the patients, we feel pretty comfortable that this product, this PFP does not stay around to represent any kind of a problem.

When pharmacokineticists see that kind of a picture, they say, well, we cannot have just one box here.

We have to have two boxes. So we used the simplest model that we could come up with to characterize the distribution for elimination of PFP.

The reason we fooled around with this was not so much because we care about the PFP but because we were looking for an indirect measure of the PFP release from the FS069. So we used a linear two-compartment model so it would be as simple as possible to estimate -- as you recall from that picture, we have really a pretty good feel for how fast that PFP is appearing so that must be coming from here. That is the only cleverness I suppose in this whole experiment.

PFP then in expired air would fit the two-compartment model with first-order absorption, and we had to put a lag in to make sense. The subjects and the result regression are summarized in your handout.

I only show you this complex chart because we get down to the reason we did this at all. This is the absorption rate if you will. The way we tend to think about this is in absorption half-life. So we can see in this patient there was a 16-second absorption half-life

apparently from the data, 20 seconds from this patient, and 2.2, and so forth. So, on the average or on the collective median value of the half-life of the disappearance of the half-life of the appearance of PFP and, by inference, the disappearance of the FS069 is about seven seconds. Now, that is not what I expected. That is a good deal more quick than I would have expected.

So you certainly have access to the original pictures, but -- and the one I showed you was one of the better fits, but the fits were pretty good. After a single 20-mL dose, they were fairly well-described by this approach.

In the FS069 the PFP mean conversion was seven seconds and the range was two to 21. This short initial half-life is really -- leaves us with two logical explanations. The number one possibility is a first-pass effect. When the FS069 is seen by the lungs, there is a fairly rapid conversion. The second possibility is, whether or not there is a first pass effect, there also maybe just non-constant rate of decay. Because, if you just look at a seven-second half-life, there is really not going to be much

of this substance left to account for the opacification that we see.

Now, pharmacokinetics is the study or the concern about the time course of these activities. Pharmacodynamics simply means what about the effect, what about the stuff that -- the benefit we are looking at.

Duration was among the secondary end points collected. So what we did was look at the duration of opacification as a function of the dose. You recall there were two doses of ALBUNEX and four doses of FS069 used in these studies. We have combined, for the purpose of review, 3,500 have been pretty consistently gathered together. They were done with an identical protocol. We are interested in representing -- for the purpose of labeling, we are interested in representing the truth. So combining them is what we have done here and in the other figures that Steve is going to talk about in a moment.

So you can see the duration of -- this is the median duration, the 95 percent confidence interval in each case. So these two are the dose -- this is the dose we are recommending. As you can see, the duration of opacification

is quite considerable, and the case looks pretty respectable. FS069 here, the median value is 1.9 minutes, and a 95 percent confidence interval for the five to 10-mL dose is .36 to 5.88 minutes.

So, in a sense, we think of this is as sort of the pharmacodynamic end point. Steve is going to talk about the efficacy end points in a similar fashion.

The last thing I want to touch on is what we did to look over the clinical laboratory data. We basically looked at the change. As you recall, there were data -- there were clinical laboratory on hemologic tests done before and after each testing of the FS069 and the ALBUNEX. So we basically looked at change. We looked at graphical shifts, shift table, mean change analysis and evaluation of individual patients.

The first I want to show you is of the change analysis. This happens to be for a total CPK. So we simply plot the baseline or the initial or pretreatment value here versus the final value. This is the normal range. So a patient here is a patient who had a normal or who was within the normal range of value before and a little bit higher

after or abnormal after and so forth.

So what we are obviously interested in are patients like this, who show up with a particularly high post-CPK value that they did not have pre. This particular patient had had a cabbage procedure, so we can blame this one in the surgeons also.

[Laughter.]

DR. SPYKER: Shift table, as you can gather from the name, simply looks at what is the baseline value and the post-value. We see, for example, 164 patients. These patients had a normal pre and post. This patient had a high pre and a normal post, and so forth. You can do statistics on that, but we really are just looking for an overview of what is going on with the laboratory data.

Of course, we looked at the mean change analysis. What is the average value before and after? It is not uncommon to see a statistically-significant difference here in terms of confidence intervals. But we concurred in general with the sponsor that the statistically-significant changes were not clinically-significant. Of course, we looked at individual patients, when they were like that

patient I mentioned with a high CPK, and we looked at the case report forms and number of cases.

So the bottom line, in terms of hematology and chemistry, we did not find any problems.

The last thing I am going to touch on is adverse events. The thing that we want to do with adverse events is describe the data set, talk about any fatalities which, in this series of studies they were none, and tell about the observed adverse events and the expected adverse events.

There were 303 patients. 274 received FS069 and 3,000 -- 3,500 is what we decided were the most relevant in terms of the labeling. In that case, 203 patients -- 199 received FS069 and 200 ALBUNEX. As I mentioned, no deaths.

What we are recommending for the labeling is not unlike what the sponsor said. We would propose, since it was a crossover study and since, in fact, overall, there were really certainly no more than statistically -- than there were with the ALBUNEX, this is what we are proposing to put on the label. We are not proposing to have the cut elbow, but basically everything else on here.

[Laughter.]

DR. SPYKER: Without further ado, I would like to summarize and turn it over to Steve.

What I tried to tell you then is that this compound PFP appears stable in the body. It does not likely represent a toxic hazard. We saw no untoward clinical laboratory effects, adverse events. It is comparable to those that we found following ALBUNEX. The PK findings were 98 percent recovery in 10 minutes, a half-life of 1.3 minutes for PFP, a fairly rapid appearance of PFP, which is tough to explain and probably represents a first pass kind of effect.

We will hold questions until Steve has had his turn. Steve Kurtzman is a reviewer in TRD.

DR. SACKS: Dr. Steve Kurtzman.

Agenda Item: Clinical Studies

DR. KURTZMAN: Good afternoon. As has been noted, my name is Steve Kurtzman, and I am a cardiologist in the FDA Office of Device Evaluation. What I will be doing here is discussing the results of the echocardiographic study. As has been noted, the study consisted of two separate crossover trials with identical protocols, involving a total

of 203 cardiac patients. The study was carried out in 14 United States centers. Patients were given ALBUNEX in doses of .08 mLs per kilogram and .22 mLs per kilogram 30 minutes apart on one day, and FS069 .2, .5, three and five milliliters 30 minutes apart on a different day. 200 patients were given ALBUNEX and 199 patients were given FS069.

I would also like to point out that the dose of ALBUNEX when corrected for 70 kilograms showed that the .08 dose equaled 5.6 milliliters per 70 kilograms and the .22 milligram per kilogram dose equated to 15.4 millimeters per 70 kilogram. So, as you can see, the doses of ALBUNEX used were higher than the doses of FS069.

The next overhead, please.

The patients in the study range from 21 to 83 years-old. The median age was 61 years-old. As has been noted, there was an impaired function subgroup of 72 patients. This consisted of patients with cardiac dysfunction defined as left ventricular injection fraction between 20 and 40 percent or a pulmonary dysfunction defined as clinically significant bronchiectasis, chronic

bronchitis, asthma, emphysema, or pulmonary hypertension.

Regarding the end points, the safety end point was all adverse events. One of the primary effectiveness end points was endocardial border delineation, or EBD.

The secondary effectiveness end points were, one, left ventricular opacification, or LVO, measured by left ventricular filling and by left ventricular P contrast intensity; two, wall motion visibility; three, contrast duration; and, four, doppler signal enhancement.

For the echocardiographic study, there was an independent safety review committee which evaluated all adverse events. There was also an independent core laboratory blinded to test agent dose, and patient clinical history which assessed the echocardiographic images.

Regarding the safety results, as Dr. Spyker has already reviewed with you, he presented a summary of adverse events. I will not go over that any further than what he has already told you. But we would also like to point out that there were no differences in the frequency of adverse events between the impaired function subgroup and the remaining patient population.

There were two figures regarding the effectiveness results, which we would like to show you. These I will show you in a minute. The first figure, figure five, is the present improvement in endocardial border delineation, with increasing dose of FS069 for all patients and for the impaired function subgroup.

The second figure, figure six, is the percent of patients achieving greater than or equal to 67 percent and achieving 100 percent left ventricular filling with increasing dose.

This is figure five, the patients with one or more segments improving in endocardial border delineation for FS069. As you can see, the improvement was similar for all patients and the impaired function subgroup. At a dose of three milliliters, which is the dose that the sponsor proposes to give, the improvement was 93 percent for all patients in the impaired function subgroup.

Figure six is the patient achieving greater than or equal to 67 percent left ventricular filling and 100 percent left ventricular filling for FS069. As you can see from the figure, across all four doses of FS069, more

patients achieved greater than or equal to 67 percent left ventricular filling than achieved 100 percent left ventricular filling.

At a dose of three milliliters, 95 percent of the patients achieved greater than or equal to 60 or 67 percent (sic) left ventricular filling, and 87 percent achieved 100 percent left ventricular filling.

The FDA team would like to point out that regarding the results of endocardial border delineation evaluation, 85 patients at baseline had nondiagnostic, noncontrast images, which was defined as less than or equal to two over six endocardial border segments accurately seen and that three milliliters of FS069 converted 74 percent to a diagnostic image, which is defined as greater than or equal to five of six endocardial border segments accurately seen.

Regarding the results of doppler evaluation, doppler signal enhancement with the three milliliter dose was seen over the mitral valve in two of two patients. It was seen over the aortic valve in eight of eight patients, over the right pulmonary vein as it enters the left atrium

in 34 of 50 patients, or 68 percent, and over the left pulmonary vein as it enters the left atrium in 68 of 84 patients, or 81 percent.

Based on the results of the doppler signal enhancement by FS069 over the pulmonary veins, the FDA team feels that extrapolation of FS069 stopper signal enhancement capability to the four heart valves, as well as HL septal defects and ventricular septal defects is reasonable.

In summary the principal clinical study findings included the clear dose response in the primary outcome measures which were one or more segments improving an endocardial border delineation and achieving greater than or equal to 67 percent left ventricular filling and 100 percent left ventricular filling, three milliliters of FS069 converted 74 percent of nondiagnostic, noncontrast images to a diagnostic image. And extrapolation of FS069's doppler signal enhancement capability to the four heart valves, as well as HL septal defects and ventricular septal defects is clinically reasonable. Thank you.

Agenda Item: General Issues

DR. SACKS: I want to conclude the FDA

presentation with just the set of questions that we would like the panel to consider as a minimum.

First of all, I suppose, as we learned this morning, perhaps the next to the last question, which we will get to which deals with the overall safety and effectiveness might be the first one that you should consider in the course of the discussion because it renders all of the rest moot if you think it is safe and effective. But let's take them in the order we have them.

The indications for use statement as it is currently worded, as you can see, says FS069 is indicated for use in conjunction with diagnostic echocardiography in patients with suboptimal noncontrast echoes to: One, provide opacification of cardiac chambers; two, improve delineation of endocardial borders with concomitant improvement in visualization of wall motion; and, three, enhance the doppler signal.

The questions that we have are is the data adequate to justify each of these claims and are there any other issues which should be addressed with respect to the indications? That paragraph, the large paragraph we

actually deleted, and should be deleted from the material you have.

I have a little background on this second question. It may have escaped your attention. I want to highlight it. That is that these microbubbles which have a range of size between two and four and a half microns. Consider the fact that a capillary is roughly seven to eight microns in diameter and is about the size of a red cell. It is particularly the case in pulmonary capillaries that the manufacturing specifications of FS069 are that very few of the microbubbles should be as large as 10. As you can see here, 92.5 percent of them should be smaller than 10. What has not been demonstrated given that feature and given Dr. Spyker's demonstration that the vast majority of it is expelled on the first pass through the lung, that is the background to this question.

The manufacturing specifications for FS069 require at least 92.5 percent of the microbubbles to be smaller than 10 microns in diameter. FS069 is administered by injection into an arm vein, and then passes through the lungs before reaching the left side of the heart where the efficacy or

effectiveness has been judged and is to be judged. It has been postulated that the lungs filter out microbubbles greater than those 10 microns in diameter and perhaps even somewhat smaller than that and that in patients with significant right-to-left shunts, much of this filtration will be lost, allowing the larger microbubbles to reach the systemic circulation.

As it stands, the precautions section of the proposed label states FS069 has not been studied in patients with significant right-to-left cardiac shunts. These patients may be at higher risk of adverse events secondary to larger microbubbles, that is those over 10 microns, reaching a systemic circulation which would normally be filtered out by the pulmonary capillary bed. Do you believe that this precaution is appropriate and/or adequate, and do you have any alternative suggestions of ways to address this issue?

Question three, which is, of course, the one I was pointing out to you before. Has the evidence provided by the sponsor in the PMA adequately demonstrated the safety and effectiveness of the device when used for its intended

purpose?

Lastly, are there any other issues such as possible hypersensitivity or performance in specific subpopulations such as those with right to left shunts which should be addressed through post-marketing studies.

DR. HALBERG: Let me ask the panel sort of informally, would you like to take a short five or 10-minute break? The panel will reconvene at 2:30.

[Brief recess.]

DR. HALBERG: Before we proceed with the review and the discussion of PMA960045, Mr. Monahan will again remind the panel members of their responsibilities when reviewing today's pre-market approval application.

DR. MONAHAN: This will essentially be a repeat of the information I provided earlier this morning, but I think it is a good idea for the record to remind the panel of what their options are in terms of voting. The medical device amendments to the Food, Drug and Cosmetic Act, enable FDA to obtain a recommendation from an outside expert advisory panel on medical device PMAs which are filed with the FDA.

We are asking you to make a recommendation

concerning whether this PMA should be found approvable, approvable with conditions or not approvable. A recommendation must be supported by data in the application or by publicly-available information.

Your recommendation may take one of three forms. You may recommend that the PMA be approved with no conditions attached to the approval, you can recommend that the PMA be found approvable subject to specified conditions, such as resolution of clearly-identified deficiencies cited by you or by FDA staff. Examples can include resolution of questions concerning some of the data or of changes in the draft labeling.

You may conclude that post-approval requirements should be imposed as a condition of approval. These conditions may include a continuing evaluation of the device and submission of periodic reports.

If you believe that such requirements are necessary, your recommendation must address the following points: The reason or purpose of the requirement, the number of patients being evaluated, and the reports required to be submitted.

You may also find the application not approvable. The Act, section 515b(2), A through E, states that a PMA can be denied approval for any of five reasons. I will briefly remind you of three of these reasons that are applicable to your deliberations and decision. The three are, number one, there is a lack of showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the labeling.

To clarify the definition of safe, there is a reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use outweigh the probable risks.

The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

The PMA may be denied approval if there is lack of

showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling.

A definition of effectiveness is as follows.

There is a reasonable assurance that a device is effective when it can be determined based upon valid, scientific evidence that in a significant portion of the target population the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically-significant results.

The PMA may be denied approval if based on a fair evaluation of all the material facts the proposed labeling is false or misleading. If you make a nonapproval recommendation for any of these stated reasons, we request that you identify the measures that you believe are necessary or steps which should be undertaken to place the application in an approvable form. This may include further research.

Dr. Halberg.

DR. HALBERG: I again remind public observers of

the meeting. While this portion of the meeting is open to public observation, public attendees may not participate unless specifically requested to do so by the panel.

I will turn this discussion over to Dr. Domanski.

Agenda Item: Discussion, Recommendation and Vote

DR. DOMANSKI: Than you very much. I would like to start by thanking Drs. Kirkpatrick and Dittrich for a clear presentation and also to say to the FDA staff that that was really a remarkably complete workup of this application. I am most appreciative of that.

I would like to ask a few questions. Maybe some of this is really introductory. Dr. Dittrich, you may want to take some of these and kind of help me out a little bit. some of it is educational. The first thing I am going to start with is looking to the safety of it because that is certainly a key issue in dealing with this.

In going through these patients, what was the maximum blood pressure drop that occurred?

DR. KIRKPATRICK: We will need a minute for that.

DR. DOMANSKI: The next question, by the way, is going to be whether there are clinical -- whether there was

a clinical correlate to any of that to try to get a sense. I am going to think through it as though I were giving this agent or thinking about giving it. I am going to go on to safety questions to relate it back to that kind of thinking and that kind of thought process.

DR. KIRKPATRICK: Again, the end points were periodically after each of the injections and agents. For vital signs including blood pressure, there was no statistically significant change in the blood pressures.

DR. DOMANSKI: yes. I guess you have a lot of patients. I am just wondering whether there are a few who anywhere -- and this is going to go throughout the questioning -- whether there were a few who came to grief in some way that is not immediately obvious from that statement.

DR. KIRKPATRICK: I would say no. It is important to remember that many of these patients were hospitalized and had entered current illnesses.

Again, to reiterate, 36 percent fit into that impaired function subgroup, many of whom had cardiomyopathy, be it ischemic or congestive. So to see changes in vital

signs, for instance, at a time at least 48 hours after the device was given --

DR. DOMANSKI: I guess, as a practical matter, I am not so worried about what happened 48 hours later, but I am just really more interested in the nearer term.

DR. KIRKPATRICK: Well, effectively, we saw no acute effects in vital signs and hemodynamics that the investigators reported. Maybe this is an opportune time to ask Dr. Michael Picard, who is from Massachusetts General Hospital, who was one of the investigators in the study, was there for this study, for the injection of both agents, to comment directly to you.

DR. DOMANSKI: Sure.

DR. KIRKPATRICK: It can get specific to his impression. Dr. Picard.

DR. PICARD: Good afternoon. I am Michael Picard. I am an assistant professor of medicine at Harvard Medical School, and associate physician at Massachusetts General Hospital and Associate Director of the Echo Lab, Echocardiography Lab at Mass General. I should also add that I am a member of the IRB at the Massachusetts General

Hospital. I was an investigator on some earlier preclinical studies with FS069 and an investigator in the phase 3 study. I am also being compensated for my time here today.

I cannot tell you the exact details of the 12 patients that we had enrolled in the study. My impression - - we certainly did not see any clinically-significant changes in blood pressure throughout the five or six-day observation period in any of the patients, whether it be in the ALBUNEX time period of the drug administration or the FS069 administration. I actually would probably be more concerned about tachycardias potentially in this group of patients who had some significant clinical illnesses particularly the cardiomyopathy group. They might have more of a problem handling a change in their heart rates. Again, we do not see any differences in heart rate.

DR. KIRKPATRICK: And, if you would like a further answer, I can -- we have clinical write-ups on the three people who were thought to have clinically-significant changes in blood pressure, but only three.

DR. DOMANSKI: Okay. Maybe you could tell us a little bit about those. Thank you very much.

DR. KIRKPATRICK: Patient 3112 has a baseline blood pressure of 138 over 73. Forty-eight hours after FS069, had a follow-up reading of 92 over 48. So, again, this is at 48 hours. If you would like me to go on --

DR. DOMANSKI: No, not on that one. What about the other two?

DR. KIRKPATRICK: Patient 3204 has a history of hypertension and congestive heart failure with highly variable blood pressures who had a baseline pre-FS069 reading of 135 over 72 and a pre-number four FS069 injection of 92 over 40. This patient was on diuretics with extremely variable blood pressures from 92 over 40 to 181 over 87. No ADEs were reported and oxygen saturations were stable throughout.

In the 3,500 patient 5318 had a clinically-significant change in blood pressure with a baseline reading on 12-20-95 of 115/63 and an elevating reading of 156/98 a day later.

DR. DOMANSKI: Okay. Good. That answers my question with respect to that.

All right. I guess the next question is, I would

like to -- actually, the graph that was passed out by the panel does it very nicely. I do not know if you are talking about the FDA staff. They do it very nicely. There were at least two people with marked elevations of CPK. I wonder -- let's see, I have the reference number for one of them in FS1000 it was subject three. I am not sure which one that is on this graph. We are told that one of the elevations was in the setting of a coronary bypass. I wonder if you could tell us about the CPK elevation and the CPK_{NB} specifically?

DR. KIRKPATRICK: FS1000 was performed in normal, so you must be referring to --

DR. DOMANSKI: I may have the wrong number then.

DR. KIRKPATRICK: But there are no bypasses.

DR. DOMANSKI: There are two people in figure four who have marked elevations of CPK. I guess I would just like to know whether it was the NB fraction or whether -- you know, what happened -- kind of what the time course was and decide whether we think it was related to the agent.

DR. KIRKPATRICK: That figure was actually total CPK. The patient -- there was a patient who between first

and second agent underwent coronary artery bypass surgery, obviously for endocurrent illness that had not been related to this study. That patient 5107 had noncontrast ALBUNEX injections on 2-7-96 with a CK of 19. He underwent coronary artery bypass surgery on 2-8-96. Then, on 2-11-96, underwent FS069 study with the baseline pre-FS069 value of CK having gone from 19 to 933. After FS069 on follow-up, it was 164. So you can see actually the CK -- maybe that is not the one in the upper left.

DR. DOMANSKI: Well, there are two of them here. One goes from about five -- it looks like it goes from about 540 to 860. That is not bad. And then there is the one in the upper left-hand corner on this thing that went from something that is normal to over 900. Those numbers do not exactly -- I wonder if these are the same page.

DR. KIRKPATRICK: I cannot put my hand on those because the investigator determined whether or not values were related to endocurrent illness or not. If they were, we did not specifically review those outside -- as specific write-ups.

DR. DOMANSKI: You know, the reason for asking the

question is obviously most people did well with this agent. The question is embedded in these studies somewhere a group of people who did not do well? Obviously, you know, these are kind of major elevations. It would be interesting to see whether they were related to the agent. It raised a little bit of a concern about it. Okay.

DR. KIRKPATRICK: I certainly believe that having had an intervening coronary artery bypass surgery --

DR. DOMANSKI: No, I think the bypass one I will give you, but there are two here who do not seem to fit those numbers, the numbers you are quoting.

DR. KIRKPATRICK: We may have found another of the outlier.

Patient 5311 had the following clinically-significant total CK value from baseline through 48 hours after injection of the second agent, ALBUNEX -- sorry, that is after ALBUNEX, which was all MM.

DR. DOMANSKI: It was subject 32 in 1,000, by the way. I just had the wrong number. Those were supposed to be normal patients.

DR. KIRKPATRICK: That is right. We will look

that up. We have subject number three in the 1,000.

DR. DOMANSKI: Well, I am reading, yes, subject three. Okay. Go ahead.

DR. KIRKPATRICK: That patient entered with a baseline CK total of 95 units per liter. At two hours post-study, the CK total was -- and I should point out that that baseline CK could have been done several days preceding, not immediately before. They used the screening lab CK to enroll. At two hours post-study, the CK total is elevated from 2,321. At 24 hours, the total is 1,160. During the administration procedure of 0.5 and 5 mLs of FS069 the subject is very nervous and visibly shaken. All other safety evaluations were normal with the exception of SOT, which was elevated to 84 units per liter at the 24-hour follow-up. The subject reported no ADEs on study or post-study. He was one of the subjects selected for the immunologic testing who returned once in the three weeks post-study. The subject returned to the site two weeks post-study, and the CK total was 114 and the SGOT 16.

DR. DOMANSKI: Do we know what the MB spike was?

DR. KIRKPATRICK: It was zero.

DR. DOMANSKI: No, no, no. I mean when it went up, when the total CPK was high, was the MB high?

DR. KIRKPATRICK: No. It was all MM.

DR. DOMANSKI: It was all MM. Okay. All right. That answers that.

Now, the other thing is that there were a number of patients whose oxygen saturations decreased and appeared to do so reasonably acutely. How many of those people had clinically-recognizable changes? How much of that drop in O2 SAT was actually associated with anything?

I wrote down an example of 32 in FS1000. Were there symptoms that went with these O2 SAT drops?

DR. KIRKPATRICK: In the FS1000 there was one individual who dropped from a normal value, in the high 90s to 85 percent. I was present for that study. In that study, we were collecting expired air while imaging and trying to obtain best possible images. The patient stated that she was attempting to assist the stenographer -- because we all know during ultrasound of the chest, people are asked to either breathe a certain way or limit respiration. She had been asked to do that and at the same

time was trying to complete an expired air collection sample.

[Laughter.]

DR. KIRKPATRICK: And, in addition, rotate a table dish on a stick.

[Laughter.]

DR. KIRKPATRICK: She started to cough and her oxygen saturation did drop. She began at 96 and at six minutes post-injection was 87 and at eight minutes it was 96 percent. There were no other particular values in her except to say that I was present for that. We actually specifically asked our pulmonary consultant, Dr. Jack Clausen because I was not familiar with what kind of value drop would be acceptable in a scenario where a patient is now coughing after going through these mechanical efforts. Dr. Clausen's impression was that that is not atypical at all during a coughing spell for that to happen. He is here if you would like to ask him anything further.

DR. DOMANSKI: You know, I do not think so. I think that was basically clear to me.

The reason I am pushing this 02 sec business a

little bit is I wonder -- I am going to ask you about a couple of special populations and I think the panel is going to need to give some thought to a couple of special populations. One of the ones that comes to mind is people with primary pulmonary hypertension or very severe pulmonary hypertension where embolizing the bed with this albumin might be a problem.

Mike, can you speak to that issue at all?

DR. KIRKPATRICK: Actually, we certainly can. I think it is appropriate for Dr. Clausen to address. Because, along with that study we had him review the pulmonary aspects of the entire PMA.

DR. DOMANSKI: Great.

DR. KIRKPATRICK: We know this is an issue -- potentially more of an issue for the non-encapsulated contrast agents. We believe because of the albumin shell technology we have a controlled microsphere size. But we address that specifically to answer issues potentially about albumin. So, if Dr. Clausen would come up please.

DR. CLAUSEN: I am Dr. Jack Clausen from UCSD. I am a Professor of Medicine there. I am being reimbursed for

this trip from MBR. I have functioned with him as a consultant.

In answer to your question about the oximetry value suddenly dropping, we have to remember that the oximetry technology relies on pulse and pulse pressure. Basically, that is why it is called the pulse oximeter. So, if a patient is coughing and raises their intra-thoracic pressure, it is not at all unusual for you to get an isolated drop in the saturation reading.

The pulmonary function that was looked at included spirometry, which is a sensitive indicator of restrictive as well as obstructive defects or pulmonary malfunctions associated with injected materials that might be resulting.

In the FS1000 study on normal subjects, there was no effect noted from the FS069.

In four of the studies, oxygen saturation was also done.

Just one follow-up on spirometry too. It was performed in the FS6000, which included subjects that had some dysfunction.

There was a problem at the contract laboratory.

The person who was trained to do it left. The person that replaced that person I think did not do the spirometry properly. I reviewed that data and the company had decided that the spirometry data was invalid, and I agreed totally. It was just done not according to the way it should be done.

The more sensitive test really in terms of looking at embolization would be the oxygen saturation. It would be especially sensitive in the patients with dysfunction either with cardiac or especially with pulmonary disease. Again, in all of those studies there was no effect. There were actually surprisingly few isolated drops in saturation considering the number of patients that were studied.

DR. DOMANSKI: You have now had some experience with this agent. You are an expert in pulmonary medicine. If you were seeing patients, is there a group of patients who you would hesitate to give this to? For instance, if you saw a patient with primary pulmonary hypertension at very high levels of pulmonary pressure or high levels of pulmonary pressure for other reasons, would you have some hesitation about this?

DR. CLAUSEN: I do not do the catheterization, so

I think you would want to talk to some of the cardiologists. We do see a number of patients at UCSD who have chronic pulmonary emboli who come in with high pulmonary vascular pressures. I think that the volumes of this material that are being administered are very small and are smaller than the contrast material that we use with angiograms, for example. So I would not have a problem with that in patients with pulmonary hypertension.

DR. DOMANSKI: Do you have any experience in patients with very high pulmonary pressures in this study?

DR. KIRKPATRICK: Many of the patients with cardiomyopathy, the cardiac myopathy subgroup had severe LD dysfunction and pulmonary hypertension secondary to the left atrial hypertension. That was very common. And, as well, a subgroup of the pulmonary patients of those 36 percent could be enrolled based on pulmonary hypertension alone. There are a smattering among the pulmonary hypertensive of that group.

If your concern is about emboli, micro-emboli, then perhaps the best answer -- before we do maybe, Dr. Clausen, Jenifer, if you would put up those O2 sets, he

could sort of give the oxygen saturation. So you see the kind of trends we have. This is the FS3000. Maybe Dr. Clausen will comment on the --

DR. CLAUSEN: They are very dull.

[Laughter.]

DR. CLAUSEN: It is really hard to see any kind of a trend at all.

DR. KIRKPATRICK: Show the other study. Again, these are done every two minutes you see through eight minutes and then 10, 20, and 30 minutes after the final five-mL injection. I think Dr. Clausen pointed it out. Remember at 3 mLs we are talking about 100 microliters of total gas. That is a very small volume.

I think though to answer the issue of albumin and embolization, I would ask Dr. Calvin Saravis to step up who is the individual who performed the immunology studies for us. I think, since we know that micro-embolization activates different pathways including complement, perhaps that will answer it in actually not an indirect way at all.

DR. SARAIVS: I am Calvin Saravis, Associate Professor of Surgery and Biochemistry at Harvard Medical

School. I was paid to do the immunological studies of 1,250 and the 6,000. Included in the 6,000 were five patients who received FS069 who had pulmonary disease. Using highly sophisticated tests of complement split products, IC3B for the C3 confer days and looking at the SC5P9, the end stage of the mac complex, I can unequivocally say that none of these patients have any complement activation. And complement activation is known to occur within respiratory patients who have emboli.

DR. DOMANSKI: Good.

DR. SARAVis: Yes.

DR. DOMANSKI: That answers that question. In fact, while I have got the immunology expert here --

DR. SARAVis: Right.

[Laughter.]

DR. DOMANSKI: -- let me --

DR. SARAVis: That is not fair.

[Laughter.]

DR. DOMANSKI: It was going to be the next question anyway. You know, I would like -- and maybe it is a bit of a primer for me, if you will, but one of the things

that certainly could occur that might stay one's hand in terms of routinely using an agent like this, is a concern about hypersensitivity reaction. I think it is unusual to have a hypersensitivity reaction to albumin that occurs. I wonder about people who have had a relatively recent transfusion with this kind of protein for other reasons or an individual who has recently had one of these studies. Is there -- in your view, is there an added risk to them?

DR. SARAIVIS: Not at all so. I had the opportunity to take a look at patients, normals, as well as normal people who were immunized intravenously with FS069 at least a year before. Looking at the amnestic response, the recall response, they had no reaction either immunologically, that the cytokine reaction, IL1, IL2, tumor necrosis factor. We looked at continent activation, and none of them, they were completely normal.

DR. DOMANSKI: So your sense is that having had this material given to them at some time in the past including recently is not an added risk factor for beyond what --

DR. SARAIVIS: Not at all.

DR. DOMANSKI: Good. Thank you.

DR. SARAIVIS: Thank you.

DR. KIRKPATRICK: Dr. Domanski, I will refer you to the overhead in which there have been publications with ALBUNEX, effectively the same albumin technology in which there is safety demonstrated in repeat injections.

DR. DOMANSKI: Good. Okay, thank you.

I have one other question about special populations if you will. That is the group that has a demonstrable right-to-left shunt. I wonder about the risk of injecting these spheres in them from the standpoint particularly of neurologic events. Can you speak to that issue?

DR. KIRKPATRICK: I would be happy to.

I think, in order to do this, it is important to reiterate the device characteristics of both ALBUNEX and FS069. Remember that by composition one is made with one percent albumin and the other five percent albumin. And the other substantial difference is that ALBUNEX is filled with air; FS069 is filled with perfluoropropane.

Importantly, in the mean size range, you will see

that they are effectively similar size range and most importantly the manufacturing process and, again, these are pre-formed albumin microspheres filled with a gas. They are the same at the time of manufacture when they are -- or effectively the same immediately before being given to the patient.

We know that 92.5 percent of them are equal to or less than 10 microns in size. That is true for both ALBUNEX and FS069. Again, to reiterate, we are talking about a hundred microliters of perfluoropropane in a 3-mL injection.

Now, if we could turn the tape on please and turn the lights down. We did not specifically study patients who had right-to-left shunts in the two studies, the FS3000 and the 3500. But what I am going to show you -- hit the pause, please -- is that this is a patient with an atrial communication and this is the injection after 5 mLs of FS069. So what you are going to see is an effect of contrast passing through that right to left communication which we will show you visibly.

This patient received 5 mLs of FS069 and had one hour later noted some flushing, but had no other adverse

device events and no other changes in laboratories.

Let's run the tape please. This happens fast now. Through a shunt we see -- before it comes through the lungs -- through a shunt we see it down at the atrial level. If I had my pointer, I would fire some -- it is entering now. Did you see it enter through the right atrium? Let's go back there. Stop it here. Whoa. Okay. Play, and I will have you stop again. Okay. Stop. Interatrial septum right here. We are going to see the communication here. It takes about six beats to transit the lung so anything passing before that, as soon as it hits the right heart is from a right-to-left shunt. Go ahead. This is a 5-mL injection. There it is. That is the shunt.

Okay. Now we see attenuation from the ebolis that comes through the lungs, the more attenuation here. Let's run.

Here is the next one, again, another patient. This patient received 5 mLs. He has no adverse device events. Specifically, these patients are asked immediately after and are evaluated continuously.

Floppy interatrial septum. Injection coming here

now, and there is a big blast through. Then, as it enters from the lungs, the bigger blast comes through. Tape off.

The next overhead please. Now, importantly, and I think the point of showing you the similarities between ALBUNEX and FS069 is that study 13491 under ID #G920008 was performed in which intra-aortic ALBUNEX was given. Now, I want you to forget about a right-to-left shunt at the atrial level. We are talking about an injection of six mLs of ALBUNEX, cumulative volumes of 24 mLs directly into the aorta, literally a heartbeat away from the brain. Those patients reported three minor and transient ADEs, none of which were changes in CNS function or are related to the direct arterial injection.

DR. DOMANSKI: How was CNS function evaluated?

DR. KIRKPATRICK: Those were evaluated continuously. This happened to be part of a cardiac catheterization study.

DR. DOMANSKI: How was the CNS function evaluated?

DR. KIRKPATRICK: No. They were not undergoing EEG. They were in the midst of a cardiac catheterization.

DR. DOMANSKI: Oh, it is just the symptoms that

they did or did not report?

DR. KIRKPATRICK: That is correct.

DR. HALBERG: I think the concern is that FS069 will hang around a lot longer than ALBUNEX.

DR. KIRKPATRICK: I agree. We would never make the comparison from intravenous injections. ALBUNEX given with the same size specification directly into the aorta lasts, persists long enough to product myocardial profusion because that is what this study was about and produce no safety issues with regard to the heart. But I was answering specifically with regard to CNS.

DR. DOMANSKI: Okay.

All right. What I would like to do at this point is perhaps go around to the other panel members and ask them to discuss or ask questions as they feel appropriate. Should we start with you?

DR. DESTOUET: I have no questions.

PARTICIPANT: No questions.

DR. CHOYKE: I have a couple of questions. The rate of administration of 1 CC per second, is that -- first of all, how was that derived, and is it dangerous to inject

3 CCs per second or 5 CCs per second?

DR. KIRKPATRICK: We did not study faster rates. The genesis of this was because ALBUNEX, the first generation agent, seems to be much more fragile. It was thought initially that injecting under higher pressure at faster rates would in fact destroy the bubble and lower its -- destroy the microsphere and lower its efficacy. So in developing this, we tended to stay below that. In addition, as you saw, at rates up to one mL per second, the echogenicity of FS069 is so strong that, in fact, it may be preferable to give it at lower rates than was shown.

DR. CHOYKE: The second question. The mixing instructions are a little bit complicated. Are there any dangers except not having a diagnostic study for improper mixing of the agent?

DR. KIRKPATRICK: No. No dangers. The real issue is -- and maybe we can show the overhead of the two vials. The real issue is that these microspheres, again, are preformed, and so they exist ready to inject, except that they need to be resuspended. We can show it. On the left is unresuspended FS069. You can see that pulling up the

bottom portion of that vial --

PARTICIPANT: Can you kill the lights? Thank you.

DR. KIRKPATRICK: The white portion is in fact the microspheres. So you could see that you would have a variable concentration and effectively none if you took it from one. So the issue is just to simply role the vial to resuspend it and then withdraw.

We still recommend -- I do not need any other -- we still recommend that these vials be vented because -- and, for instance, we would not recommend that an individual fill a syringe with air and force that air into the syringe as is done sometimes with drugs, instead to vent it so that there is no big change in pressure while pulling it out. But there are no safety issues, as far as we are aware.

DR. CHOYKE: Finally, the 9 CC limit per dose. Is that per day or per life?

DR. KIRKPATRICK: Oh, no.

[Laughter.]

DR. KIRKPATRICK: That is per study based on the 8.7 mL cumulative volume in the phase three study.

DR. CHOYKE: So you would repeat it in an hour?

DR. KIRKPATRICK: If there were an indication to follow up after some procedure or something, yes, effectively.

DR. CARSON: I have no questions.

DR. DOMANSKI: Dr. Lerner.

DR. LERNER: I have two. One is for patients with neural thrombocines. Does that delineate the thrombins?

DR. KIRKPATRICK: Well, I showed the one where we suspected artifact. But we do not ask the investigator specifically that question. They may have noted it in their reading, but it was not a part of our file.

DR. LERNER: The second question was spurred by Dr. Sacks in the beginning about these little particles acting as antennas. It makes me wonder if they are scattering across sections that are so much larger than their physical size, could this cause errors in delineating heart -- the endocardial order, in other words, the echo is perceived to be coming from somewhere where they are really not present?

DR. KIRKPATRICK: Well --

DR. LERNER: And is the gold standard for itself?

DR. KIRKPATRICK: Actually, we did a gold standard study, and Dr. Ann Kilum, from MBI, will show you the results of that. That question was asked initially with ALBUNEX.

DR. LERNER: Okay.

DR. KIRKPATRICK: You can imagine, as we got into ultrasound contrasts, there were some people who were pretty confident they knew exactly where the endocardium was. So when contrast agents first came along, we had to prove this as a principle.

DR. KILUM: Dr. Ann Kilum, from MBI. This study was done actually by Mallinckrodt Medical when ALBUNEX was being filed because there was a concern as to whether or not you could actually detect the endocardial border. This was done in dogs where five stainless steel helices were implanted using a catheter on the endocardium with fluoroscopy. The placement of the helices were independently measured during echocardiography before and after ALBUNEX and then postmortem gross examination. The results of these studies suggested that there was objective evidence of enhanced visualization of the actual endocardial

surface in the presence of ALBUNEX microspheres. We would assume that, based on the same characteristics in the myocardium, that this would be also true for FS069.

DR. ALAZRAKI: I have a few questions. Under what conditions will these particles clump?

DR. KIRKPATRICK: None. But we have no evidence from in vitro testing that they clump or aggregate in any way.

DR. ALAZRAKI: Do you do regular quality-control to make sure that they are the size on a routine basis for each preparation?

DR. KIRKPATRICK: Oh, yes, ma'am. Perhaps I could have Dr. Ed Jablanski discuss the issue of aggregation of our microspheres for you.

DR. JABLANSKI: I am Ed Jablanski from MBI. I have viewed FS069 microspheres in hundreds of microscope fields. This slide you have already seen. FS069 will float to the surface of a vial that is left undisturbed and literally compact itself into a tight layer. If aggregation were going to occur, this environment would certainly

encourage it. Upon resuspension into a uniform white liquid and sampling and viewing microscopically, hundreds of fields looked just like this. There appears to be no aggregation, there appears to be no interaction, no repulsion, no attraction in just individual spherical bodies that in a dynamic situation float around the slide and bounce off of one another without any apparent interaction at all.

Yes, we do control or assay and QC for mean size distribution concentration for every single one.

DR. ALAZRAKI: Have you done any experiments changing pHs to see what happens?

DR. JABLANSKI: Within the physiological range certainly. But I have never observed any aggregation at all in FL069.

DR. ALAZRAKI: Okay. The particle size that you have given us is 92.5 percent less than 10 micrometer. At 10 micrometer these would be trapped in the pulmonary capillaries. At four to five micrometer they probably would not be trapped in the pulmonary capillaries. So I think the more important figure would be what percentage of them are

smaller than five micrometer in diameter.

DR. KIRKPATRICK: We have size distributions. I do not think that I have those right at-hand.

DR. ALAZRAKI: There are only about 10 patients that I recall who had serious or who had pulmonary disease who were studied; is that correct or are there more?

DR. KIRKPATRICK: That was in the FS6000 study. There were 50 subjects of whom 10 had pulmonary disease and five of those received FS069 20 mLs. But of the two pivotal phase three studies, 36 percent comprised the group, I think 85 total, and who either had cardiac dysfunction and/or pulmonary dysfunction.

DR. ALAZRAKI: Can you give us an idea of how severe pulmonary dysfunction was in this group of patients whom you define as pulmonary dysfunction?

DR. KIRKPATRICK: Well, not to characterize too strongly the population who goes to the VA, but literally, the biggest -- a substantial proportion, our biggest enroller was a VA who enrolled 30 patients. These were patients with severe emphysematous lung disease disabled by their pulmonary disease. This was not 80 percent of

predicted tidal volumes or forced expiratory volumes. They were people carrying significant limitation from that pulmonary or cardiac disease.

DR. ALAZRAKI: Based on the number of particles that are being injected, I think they are about two orders of magnitude more than let's say the number of particles injected for a lung scan. If more than 10 percent of them are going to be trapped in the pulmonary arterioles or pulmonary capillary bed, that would be a lot of particles, a lot of capillaries being compromised in severe pulmonary disease. If you reduced the dose in patients with severe pulmonary disease, would you have an effective study?

DR. KIRKPATRICK: You saw efficacy superior to ALBUNEX for the 0.2 mL dose, including the impaired function subgroup. The answer to that is unequivocally yes.

DR. ALAZRAKI: So you could reduce the dose by a factor of 10, from let's say 3 mL to 5 mL to .2 mL or something like that and still get efficacy?

DR. KIRKPATRICK: Again, we saw efficacy in that range.

DR. ALAZRAKI: I would think that you would want

to reduce it by a factor of at least 20 to safeguard against throwing someone with severe pulmonary disease over the edge just based on the experience with lung scan numbers of particles.

DR. KIRKPATRICK: But I guess I would submit to you that the careful every two-minute oxygen saturation determinations without any change in specifically those patients would tell you that there is not an effect. You have already heard there is no evidence for embolization. Again, Dr. Saravis would point out that complement activation should occur and we specifically looked in --

DR. ALAZRAKI: In that group, you only looked at 10 patients with pulmonary disease, is that right?

DR. KIRKPATRICK: That is right.

DR. ALAZRAKI: That is a very small group.

Do you know is there data on the 27,000 studies that have been done with ALBUNEX in terms of any kind of serious reactions?

DR. KIRKPATRICK: I have those -- a copy of -- just a minute please. Before I move to that, it is probably good as well to reiterate that these microspheres' half-life

-- we talked about the perfluoropropane and its short half-life. The duration of contrast effect is around the four-minute range. These are not microspheres lasting. We anticipate that within the body that is occurring regardless of where they are not just in terms of their ultrasound contrast effect. So I am not sure you can make an analogous comparison to the particles used for a lung scan.

DR. ALAZRAKI: If you throw someone over the edge with very compromised pulmonary function, it will happen right away.

DR. KIRKPATRICK: That is true. But, again, that was when we were measuring people's oxygen saturations, during every two minutes after those injections and up to 30 minutes even after five mLs. I have the complaint analysis through 2-7-97 for ALBUNEX. And the predominant discussions were vial appearance being unusual, a problem with the core, the stopper mainly, and failure to opacify. But we see no issue relative to those questions, adverse device events related to the pulmonary effects.

DR. ALAZRAKI: Another question related to the perfluorocarbonate. The pharmacokinetic data indicated that

two percent, approximately 98 percent is recovered in the expired air, two percent presumably not. The question would be is there any chance that that two percent which is not recovered in the expired air approximately has any toxicity or where does it go? Where is it?

DR. KIRKPATRICK: One minute please. This is Dr. Grevel, our pharmacokineticist.

DR. GREVEL: My name is Joaquin Grevel, with PAST, Inc. in Austin, Texas. I am a consultant to MBI. My trip is paid for by them and otherwise I am paid for my services to them. I am not a stockholder in any pharmaceutical company. You definitely put me through my paces with 98 percent and what happens to the two percent. From a statistical point of view, the 98 is an estimate, so you may, if you really wanted to push us hard, take the extreme of what we have and give us a real hard time about let's say the one with 70 percent recovery, right? What happens to the 30? The point is you have to see the technique of trying to do the recovery study with blowing into bags and sampling out of bags and whatever you are handling is a volatile gas. So I would assume that the real question of

how much stays behind is very, very hard to address. I cannot here tell you what happens to two percent or to 30 percent, but I can tell you that what we have proven to the satisfaction of myself and a number of others is that, if I could express it in plain language I would say everything has definitely been recovered and there is no evidence from the overall picture that there is anything left behind. There is no evidence in this recovery study that we should be concerned that any PMF is left behind in the body and has not been recovered during the 10 minutes. Everything else is related to the measurement issues.

DR. ALAZRAKI: Would it be worthwhile just to confirm that to perhaps do some studies with a radioactive fluorine compound which exchange reaction and get it onto the PF₄ and confirm that really there is nothing left anywhere?

DR. GREVEL: Without using the bubbles or with using them?

DR. ALAZRAKI: With or without.

DR. GREVEL: Without the bubbles you have a real gas that would be dangerous. I would rather have the PMF

packaged in the bubbles.

DR. ALAZRAKI: Yes, fine.

DR. GREVEL: But, at any rate, it is a gas that would always be exhaled through the lungs. So the measurement problematic of this study in terms of sampling exhaled, hair, air accurately remains whether this is radioactive labeled or not. So we are not really here in a quandary because of detection limits of our assays where a radio label would give us an advantage. We are potentially limited simply by the physical difficulty of performing that study. That study could be reported and I would guess that the confidence intervals would be similar to our estimate, and the point estimate could end up being 102 and you could twist the whole thing around and ask where do the two additional percent come from.

[Laughter.]

DR. ALAZRAKI: That is an indication that maybe there are some problems with the measurements, with the assays.

DR. GREVEL: With the physical contact of that study, I personally was delighted to the degree that it came

out. If you want to recommend to repeat this study and show it one more time that it can be done, I am confident that we can repeat this study anytime and come up with the confidence interval with very, very comparable boundaries. But the point estimate itself I cannot guarantee that it would fall again on 98.

DR. ALAZRAKI: In the patients who do have pulmonary disease, the expiration of the compound I would imagine would be a lot slower.

DR. GREVEL: As a matter of fact, we do have a slide prepared if we could put the relationship with the respiratory rate and the recovery. We did not have respiratory impairment. Mind you, these are the 10 healthy, not pulmonary-impaired. Nevertheless, I also have a slide showing how variable their breathing is. Perhaps we should show this one first.

I calculated the respiratory rate throughout the experiment and blew up one scale to make it comparable over the 10-minute observation period. Obviously, there is excitement. Blowing into this mask is not very comfortable for them. So their respiratory rates, some of them are

lower and some of them are higher. They change somewhat. Overall, however, they reach some average value. When we go ahead -- next slide please -- and plot the average value of the respiratory rate versus the percent recovery, we cannot see a relationship within these 10 subjects. As a matter of fact, it so happens that the ones with the lowest respiratory rates have some of the highest recoveries again within the boundaries of our variability in measurement. When we, however, look at the elimination half-life which is the half slide -- I will give it to you in pieces -- we see the relationship you would expect that the elimination half-life with a higher respiratory rate decreases. Therefore, it is eliminate faster. But, overall, when we look at recovery, we reach the same recovery also with those where the elimination half-life is lower. So ultimately, over the 10 minutes we do not see a relationship between respiratory rate and recovery, but we see a relationship, a slight relationship between respiratory rate and the elimination half-life within a panel of 10 healthy subjects. This has not been done in people with pulmonary disease and it is beyond me to imagine how they would do breathing for 10

minutes into these bags.

DR. ALAZRAKI: But the pulmonary disease patients I think are concerned not because of respiratory rate, but because they have fewer capillary arterial interfaces to get rid of the PF4 gas. So it would seem to me that they would not get rid of it anywhere near as rapidly, although I have no data how much and what would happen to it the longer it circulates in the blood.

DR. KIRKPATRICK: I think, if I may, again, sometimes in discussing this perhaps we start to lose site of the volumes we are talking about, even the cumulative volume of 9 mLs. The total volume of the microspheres injected is 300 microliters. Across a surface area of the lungs and even the most impaired lung, that volume is minuscule in terms of the exchange mechanism of even the most impaired lung.

DR. DOMANSKI: Dr. Hackney.

DR. HACKNEY: At the risk of belaboring close to the same issue, you have given us information about the oxygen saturation in the patient's overall, including some patients who have depressed pulmonary function. Do you have

the data on the subgroup of patients who had chronic obstructive pulmonary disease, other impaired pulmonary function and their oxygen saturation response to the administration of the agent.

DR. KIRKPATRICK: I am sorry. We do not have the specific subgroup oxygen saturation values. If they met clinical evidence, evidence per our predetermined protocol for clinically-significant -- they were written up as individual patients, but we did not subanalyze that group in that manner.

DR. HACKNEY: I guess what I was concerned about is are there significant changes in O2 saturation in a subgroup that are not seen when you look at an aggregated group?

DR. KIRKPATRICK: We do not have that. I can tell you that there were only 0.4 percent of the entire population who had a change in O2 saturation of equal to or greater than 7.5 percent. So, if they were all impaired function, all pulmonary, it was only five patients out of the 83. But I cannot tell you if they were.

DR. HACKNEY: Along the same lines, your

spirometry data ended up you only have data from one of the normal subject studies and the study in which you were to have collected spirometry from patients, including some patients who had pulmonary disease, there was a problem I gather with the spirometry and you decided it is not reliable and worth reporting. Was there any consideration to doing a study in which you did successfully collect spirometry? I do not think it is real hard to do that. I was sort of surprised that you attempted 50, and for some reason it did not work, and instead of doing it somewhere else, you just decided to drop that issue I gather.

DR. KIRKPATRICK: Well, we considered that, but decided to pursue through a consultant expert, Dr. Clausen, the issue of whether in fact we had already used by following closely-monitored oxygen saturation and adequate tests then, as you heard him say, and we could have him reiterate the oxygen saturation in a disease population. Because of their position on the oxydissociation curve, it is actually more sensitive. If you think about it, the spirometry testing is much more an airway test. Isn't the real question about the ability of oxygen transfer? So

oxygen saturation ought to be and we feel is the best test.

DR. DOMANSKI: Well, I asked a number of questions about safety. The reason I did not ask any about efficacy is I think, while one could say things like it is pretty hard to completely blind a study like this where the persistence is there and so forth, the truth is I think the efficacy is pretty clear in this agent and at least in my view.

Also, I think a very careful job has been done in looking at safety. I am going to end up making a motion here for approval. The question -- I think that the question and one that I would like the panel to consider a bit is whether or not any post-market surveillance is indicated.

You know, it is very easy for us, in my view, to say, look at this, look at that, but it certainly becomes a heavy order for a company unless there is a good reason for doing it. My sense, after listening to all of this and being concerned about some special populations, like people with very elevated levels of pulmonary hypertension, and people with shunts, is that there are few data anywhere it

seems to suggest that there is a risk involved. I think that where there is a suggestion of that, even if it is a relatively small suggestion, I would have a high level of enthusiasm for tracking the thing in great detail. I am hesitant to put that sort of burden out there in the absence of any evidence just because there is a theoretical possibility that maybe somewhere, someday, somebody could possibly have something that might be related.

So I would note that I think that this, by the way, is remarkable. I have been on the FDA Devices Panel for years. This is a very carefully worked up application. I mean, gee, it really is. I would move approval without conditions.

[The motion was duly made.]

DR. GRIEM: Second.

[The motion was duly seconded.]

DR. HALBERG: Let us just go through the discussion points very quickly also.

Jeff, you may want to put those up.

DR. DOMANSKI: In fact, let's -- perhaps I could ask the FDA staff -- I would like to go through these one by

one and make sure that the questions that have been posed have been answered to your satisfaction. I guess what I am -- who should I ask from FDA to speak to this? I think, going through number one, indications for use statement as it is currently worded in the labeling, is shown there. From my standpoint, I think the labeling that has been requested seems entirely appropriate. Does FDA staff have remaining residual questions about that?

DR. SACKS: There is only one question, I guess, that may be relatively unimportant from the panel's point of view, but that is the location of the phrase in patients with suboptimal noncontrast echoes. You will note the company proposed that as the fourth bullet rather than putting it up at the top. Other than that we have no other questions unless somebody --

DR. DOMANSKI: Well, I guess, that one could ask - - let's think about the logic of that. If you put it up there, then it becomes with suboptimal non-contrast echoes and then only those things, cardiac chambers, endocardial borders and enhancing the doppler signal. In fact, somebody looking for a shunt might in fact give it to look for a

shunt and that would not really be part of the indication since there are only suboptimal studies for that. So actually, I think it is better as a fourth bullet because it provides them with a more general indication. So that is at least what I would recommend.

Does anyone on the panel feel differently relative to that?

[No response.]

DR. DOMANSKI: Eight. Adequate to justify each of these claims. I think we have answered that.

Are there any other issues which should be addressed with respect to indications? I do not think so. It is pretty straight forward.

[No response.]

DR. DOMANSKI: Please, if anyone on the panel feels differently, please speak up.

May I have the second one? Let's see. Manufacturing specification for FS069 require at least 92.5 percent of the microbubbles be less than 10 microns. If it is administered by injection into an arm vein and then passes through the lung through reaching the left side of

the heart, it has been postulated that the lungs filter out microbubbles greater than 10 microns in diameter in patients with significant right to left shunts. Much of this filtration will be lost allowing larger bubbles to reach the systemic circulation.

Precaution section of the proposed label states, and then I will not read it again. Do you believe that the precaution is appropriate and/or adequate?

PARTICIPANT: Yes.

DR. DOMANSKI: My sense is that it is entirely adequate. Is there anyone on the panel who feels differently? Dr. Alazraki, could you speak to that?

DR. ALAZRAKI: Yes. First, in the first part of that statement, I do not see any rationale for specifying what is greater than 10 micra. I think, if there is going to be a specification for the particle size, it should related to the size of the pulmonary capillaries and that would be more like five, six micra diameter. So I would rather see that modified to what we are talking about in terms of percentage that get across the interface.

DR. GRIEM: I would like to comment on that. I

have some \$200 of video microscopy of blood flow of which a friend in Madison provided me with tannin scanning confocal microscopy of capillary blood flow in the lung in live mice. You can see the white cells go through these capillaries along with the red cells and so forth. It is a fantastic movie. What you do is cause the mouse or -- I think it was the rat -- to stop breathing for a little bit while you put the tannin scanning confocal microscope with a water immersion lens on it and watch the actual cells flow through. White cells do go through. So they are bigger than cellular microns.

DR. ALAZRAKI: Yes, they are.

DR. GRIEM: And they sneak through.

DR. DOMANSKI: I guess that is very interesting and useful. In fact, I have a question actually that maybe will resolve it. I think that the answer is that we are not sure what that number should be. Maybe what should be done is -- let me try a sentence on everyone and see if wordsmithing helps here.

One could say that these patients may be at higher risk of adverse events. Oh well, one cannot exclude the

possibility that these patients may be at higher risk of adverse events secondary to larger microbubbles with no number specified reaching the systemic circulation. I mean, it maybe at risk, maybe at higher risk sounds more definite than we really are. I do not know if we have any evidence at all that these people are at-risk. Maybe you have to ask the company.

DR. KIRKPATRICK: Well, maybe at this point I could ask Dr. Carol Marcus, our consultant, with a lot of experience with macro-aggregated albumin, to make a comment. Because I think there are already agents that are in use and, at most, one might say these have not been studied in those patients with shunts. Dr. Marcus.

DR. MARCUS: My name is Carol Marcus. I am a nuclear medicine physician at Harvard UCLA Medical Center. I am on the Scientific Advisory Board for NVI and they are paying my way for this trip. I am also the past Chairman of this panel.

I do not think that this is a significant problem. First of all, and I share Dr. Allen Sawadski's experience with macro-aggregated albumin. I realize there that we are

blocking pre-capillary arterioles not capillaries. We are dealing with aggregates therefore that have to be about 50 microns. The number of capillaries is far, far greater, of course, than the number of pre-capillary arterioles.

Even if you look back in the literature of nuclear medicine to adverse reactions with macro-aggregated albumin, which I did some years ago, you find only three or four serious cases of possible deaths due to it back in the 1960s, early 1970s in terminal patients with severe vasculitis, a severe, severe preterminal pulmonary hypertension from birth defects, one patient with terminal mets to the lungs from breast cancer. We are talking about only maybe three patients in the whole history of nuclear medicine who ever appear to have had an adverse effect here and this is for precapillary arterioles, not for capillaries.

The other thing, of course, is that MAA has a half-life of on the packet insert six hours or maybe a little shorter, let's say three or four even. But, with our microspheres, we are talking about just a few minutes, not hours.

In the event that a patient with severe pulmonary hypertension had a bad reaction, we now have the recent regulation that came out from devices that it must be reported very quickly and we will all know about it probably within several days to a week because it is now in the regulations that it absolutely must be reported.

This is not the case for drugs. It is an extra safety feature for a device. In the event it ever happened, the company would know, the package insert would be changed, and we would not be arguing about this. So I think it really does not matter here, that it is really moot. We have no evidence of a problem. I think that theoretically there is no real reason to expect the problem. But we have the safety of the new regulations which say, if there is one, we are all going to know very fast.

DR. DOMANSKI: I am not sure that anybody was suggesting post-market surveillance based on that. I think we can leave it to the FDA staff. I think they have heard the discussion. I have some doubt, frankly, about whether the, in parentheses, greater than 10 microns makes any sense. It sounds like it may be much bigger. For me, I

would probably remove it, but I do not think it merits a motion I think. Do you believe this question is appropriate? Do you have alternative suggestions of ways to address this issue? I certainly do not. I wonder if anyone on the panel wants to discuss that.

DR. ALAZRAKI: You know, in nuclear medicine, and Dr. Marcus referred to the experience in nuclear medicine. But the practice is to reduce the dose injected when you have a patient like this with severe lung disease and certainly with right-to-left shunts. I think that that should apply here.

DR. DOMANSKI: Then perhaps we could do this. Could we hear a motion from you that we could act on relative to this labeling?

DR. ALAZRAKI: My hesitancy in the motion is that we really are acting in the absence of data. My motion would be that we need more data on the right-to-left shunt patients or subjects and on the severe pulmonary disease subjects. I have no problem with the effectiveness. My only problem with potential toxicity is in those groups of patients.

DR. SACKS: Let me just raise a theoretical point about this that may help the panel on this issue. As Dr. Spyker's talk showed, the vast majority of the injected PFP, that is the gas within the microspheres, appears in the expired air at about seven seconds. In other words, this is a first pass phenomenon. That is about the time it takes from blood to get to the antecubital vein to the lung. And yet we have also seen that the persistence of the echocardiographic effect in the left heart goes on for four or five minutes.

We grappled with this issue at the FDA about how this could possibly be. We sort of came to a tentative conclusion that there must be a subpopulation of the microspheres and there is only one parameter that differentiates one microsphere from another and that is its size. There must be a hardier subpopulation which not only makes it through the first pass, but continues to circulate through the body over and over, re-entering the left heart over and over, an average circulation time through the body is about a minute roughly. Therefore, to go on for four to five minutes, we are talking about four or five circulations

through the body.

Now, this persistence suggests that most of these that make it through on the first pass continue to make it through over and over again. It is not as though each time they pass through 98 percent are destroyed.

Having realize that, we do not know which subpopulation that is. Is it the smallest ones or is it the largest ones? I think that there is reason to assume that it is probably at the small end. This is my own theoretical bent now.

One other point about it. The largest microspheres, those that may come in over 10 microns, are the ones that are almost certainly destroyed as they enter the capillary bed. That is why they do not embolize. I think that the data that shows no immunological -- that is complement activation from any -- in other words, there does not seem to be any sign of embolization, seems to reflect the fact that even these 10 micron and above, which can be up to 7.5 percent of these microspheres, do not seem to do any embolization harm because they get broken down right away. Now, this is the only way a PFP gets out into the air

is that a microsphere is crushed and the PFP gets out of the albumin shell. So I am just throwing those out.

One other point. If we were to keep this sentence in, we would change the word microbubble to microsphere. It was pointed out to me at the break that there is a technical difference here and that is that because these do not aggregate because they are, which we had at that discussion before, they should not be called bubbles. Bubbles are capable of aggregating as we well know. So microspheres is the correct term here.

DR. DOMANSKI: You know, I think, in order to move the process forward, let me ask you, if you would, Dr. Alazraki, as the panel goes to consider your motion, could you perhaps be specific in terms of the data that you feel should be gathered? Because if it goes carry then we want some good marching suggestions.

DR. ALAZRAKI: I think we need some data on patients with right-to-left-shunt who are monitored by EEG at least. As far as the pulmonary disease population, I mean, they do have data on a group of 10 -- well, 10 who had monitoring. I would like to see that group expanded.

[The motion was duly made.]

DR. DOMANSKI: Okay. So there is a motion on the floor. Is there a second?

DR. CARSON: Second.

[The motion was duly seconded.]

DR. DOMANSKI: Okay. Is there further discussion?

DR. HACKNEY: I would like to suggest that, if we are going to ask the manufacturer to do a study looking for neurological changes, that was the idea of the EEG I assume.

DR. ALAZRAKI: Yes.

DR. HACKNEY: Most people would consider EEGs in awake patients not to be close to the most effective way to answer that. If we are going to ask them to do it, we would ask them to devise a study which would adequately test for neurologic changes. Probably EEG may not be that way. I certainly would not want to tell them that they have to do an EEG because that might be the least useful thing that might be done.

I am not sure that I would agree that that needs to be done in any case from what evidence we have seen. But, if we were going to have some, perhaps not that

technique.

DR. DOMANSKI: Let me just say one thing about that. We do though have a motion on the floor that includes EEG. Just to kind of keep things clean, do you want to --

DR. ALAZRAKI: I can amend that. I think that is a valid comment too.

DR. DOMANSKI: Can I accept the fact that your second stands? Okay.

DR. DESTOUET: I am unclear. Is this the motion for post-market approval studies or is this before?

DR. DOMANSKI: My understanding is that this is post-market surveillance that we are talking about. There is a motion for approval on the floor, namely mine, that has been seconded. This amends that if it carries.

DR. ALAZRAKI: Okay. I think I would leave that up to the FDA to consider this when we are finished anyway and leave it stand as a post-market approval kind of thing.

DR. KIRKPATRICK: I think it is appropriate to talk about what is the practice of clinical medicine, the practice of medicine before ALBUNEX, the only approved ultrasound context agent. I would like to have Dr. Robert

Vogel, our consultant from the University of Maryland, talk about existing practice and maybe put the issues of our microspheres and their size in perspective with what is done currently. Dr. Vogel?

DR. VOGEL: I am Robert Vogel. I am head of cardiology at the University of Medicine. I am a compensated consultant on the part of Mallinckrodt.

As Dr. Dittrich has pointed out, this technology is going through a rather lengthy evolution, and not only evolution from ALBUNEX to FS069, but, without FDA regulation, there has been a considerable experience in the clinical world with the use of agitated saline and agitated contrast. This is a totally unregulated practice. But what we know of it there is that there is a tremendous heterogeneity of the size of bubbles. There is a confluence and a growth of bubbles in fairly unregulated fashion.

These technologies or clinical technologies have been used for a number of years to detect shunts and have been used in patients with all different kinds of neurological, cardiac, and pulmonary impairments. To my knowledge, done appropriately, there have been no untoward

effects observed with significantly more administration of gas than would be present in the proposed study.

So I would think that -- and I agree with the panel's concern on a new type of device. We want to make sure it is safe. But I must confess that I see no reason really to be concerned about neurological events in shunt patients because we have been giving agitated saline and agitated contrast with far more content of gas to specifically these kinds of patients for many years.

DR. DOMANSKI: I can also see that a study of Robert's Rules of Order would have been in order before this. I think what we are dealing with, to try to keep this streamlined, is a motion that amends my motion for approval. It would, in effect, add the condition of a post-marketing study.

So I think the next thing to do probably is to call the question. Have we gotten down her motion? Is there someone who is actually copying this down?

PARTICIPANT: You need to restate it.

DR. DOMANSKI: All right. Let's restate the motion so that it is clear precisely what we are voting on,

if you would.

DR. ALAZRAKI: Okay. The motion is in the form of a pre-market approval study of individual --

DR. MONAHAN: Excuse me, Dr. Alazraki. Is that pre or post?

DR. ALAZRAKI: Post. I am sorry. Post-market approval -- study of individuals with right-to-left shunts with some neurological evaluation to confirm a lack of any complications and in patients with chronic pulmonary disease to confirm no adverse -- lack of adverse events using the dosages as specified.

[The motion was duly made.]

DR. DOMANSKI: Thank you. All right. Let's go ahead and vote on that. Would those voting members of the panel who are in favor of adding this requirement for post-marketing surveillance raise your hand.

[Show of hands.]

DR. DOMANSKI: Okay. I count three.

Opposed?

[Show of hands.]

DR. DOMANSKI: So the motion fails. One, two,

three, four, five.

[Whereupon, the motion was rejected.]

DR. DOMANSKI: All right. We have then on the floor a motion to approve without post-marketing -- I am sorry. Oops.

Has the evidence provided by the sponsor in the PMA adequately demonstrated the safety and effectiveness when used for the intended purpose? That is what we will be voting on in terms of the motion for approval.

Are there any other issues, such as possible hypersensitivity or performance in specific subpopulations such as those with right-to-left shunts which should be addressed through post-market studies? We certainly have dealt with that I believe. So I see no other issues for discussion unless anyone on the panel does.

Perhaps we could call the question.

DR. HALBERG: Let me first read this ditty here. We will now consider the panel's report and recommendations concerning approval of PMA P960045, together with the reasons and recommendations required by section 515C2 of the act. The data supporting the recommendation consists of

information and data set forth in the application itself, the written summaries prepared by the FDA staff, the presentations made to the panel, and the discussions held during the panel meeting which will be set forth in the transcript.

The recommendation of the panel will be approval -
- can be approval, approval with conditions that are to be met by the applicant, or denial of approval.

Let me ask you to formally restate the motion.

DR. DOMANSKI: Okay. I move for approval without any post-marketing surveillance, that is approval without conditions.

[The motion was duly made.]

DR. HALBERG: Is there a second?

DR. MONAHAN: Before the panel takes a vote on this, I would like to note for the record that there are some unresolved non-clinical issues associated with this device that the agency wants to get resolved prior to a final decision by the agency. But this should not influence your motion or approval at this point. I just wanted to note that on the record.

DR. HALBERG: Two things. One, I have Dr. Lerner's proxy. I will not vote personally unless there is a tie, but I will vote for him with his instructions.

Then I think we also need a second for the motion.

DR. CARSON: Second.

[The motion was duly seconded.]

DR. DOMANSKI: Okay. Perhaps we could see a show of hands for those who vote in favor of the motion.

[Show of hands.]

DR. DOMANSKI: Opposed.

[Show of hands.]

DR. DOMANSKI: One.

DR. HALBERG: There was one opposed and how many for?

DR. DOMANSKI: I am sorry. Let's do the for again just so that we have a counting for it.

[Show of hands.]

DR. DOMANSKI: One, two, three, four, five, six.

[Whereupon, the motion was duly carried.]

DR. HALBERG: Let me just poll the members as we go around. If you could just identify yourself, your vote,

and your reason for the vote, starting with Dr. Destouet.

DR. DESTOUE: I feel that the manufacturer has shown that this agent is efficacious and safe as specified in the indications for use.

DR. SMATHERS: Jim Smathers. I would agree that the risk/benefit looks very good.

DR. GRIEM: Mel Griem. I think that the evaluation by the FDA confirms the evidence presented by the applicant.

DR. MONAHAN: Since we are going around the table, I would appreciate it -- I know Dr. Choyke is not a voting member of the panel, but I would appreciate hearing his opinion as to the approvability of this product.

DR. CHOYKE: Thank you. I agree that it looks like a very good agent.

DR. MONAHAN: Thank you.

DR. CARSON: Sandra Carson. I am certainly convinced that the safety and efficacy of the device far exceeds the risks of the device and I am particularly impressed by the conscientious review that has been shown today.

DR. ALAZRAKI: I think it is very efficacious and certainly represents a good advance in imaging and echocardiography. I just have the concerns about the right-to-left shunts and all of those particles potentially embolizing the brain, particularly in small children. I do not see that we will exclude or prevent the use in small children of this agent. I think that we -- the FDA should get more data on the severely compromised pulmonary patients.

DR. HACKNEY: I agree that this represents an improvement upon the common bubble study that gets done so often in echocardiography. I think that the manufacturer has done a very good job of addressing the safety issues that I had which were specifically severe pulmonary impairment. I feel comfortable with the data they have given us.

DR. DOMANSKI: I am Michael Domanski. I think that the manufacturer demonstrated safety and efficacy.

DR. HALBERG: Speaking for Dr. Lerner, he voted to approve the motion without any conditions, but he did have some concerns about cumulative CNS effects in patients with

right-to-left shunts that were given more than just the 8.7 mL contrast.

PARTICIPANT: Restate the recommendation

DR. HALBERG: Okay. Let me just restate the recommendation. It is for approval with no conditions.

Does anyone have any concluding remarks?

DR. MONAHAN: Just, from the FDA perspective, I would like to thank the panel for their hard work today in reviewing these applications. I know I speak for the agency when I say that we really appreciate your efforts on behalf of these devices, and I thank everyone for coming.

DR. HALBERG: Thank you. The meeting is adjourned.

[Whereupon, the meeting was adjourned at 4:05 p.m.]